ID1058 STA REPORT

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Paclitaxel as albumin-bound nanoparticles with gemcitabine for untreated metastatic pancreatic cancer [ID1058]

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CONTAINS ACADEMIC IN CONFIDENCE AND COMMERCIAL IN CONFIDENCE DATA

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

Title: Paclitaxel as albumin-bound nanoparticles with gemcitabine for untreated metastatic pancreatic cancer [ID1058]

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All authors read and commented on draft versions of this report.

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LIST OF ABBREVIATIONS

5-FU	fluorouracil
AE	adverse event
AIC	Akaike information criterion
APC	advanced pancreatic cancer
ASCO	American Society of Clinical Oncology
BIC	Bayesian information criterion
BSA	body surface area
CA046 (MPACT)	Metastatic Pancreatic Adenocarcinoma Clinical Trial
CDF	Cancer Drugs Fund
CI	confidence interval
CONSORT	Consolidated Standards of Reporting Trials
CrI	credible interval
CRUK	Cancer Research UK
CS	company submission
CSR	clinical study report
DCR	disease control rate
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
eMIT	electronic Market Information Tool
EORTC	European Organisation for the Treatment of Cancer
EORTC QLQ-C30	European Organisation for the Treatment of Cancer quality of life questionnaire C30
EPAR	European Public Assessment Report
EQ-5D-5L	European quality of life-5 dimensions-5 levels questionnaire
ERG	Evidence Review Group
ESMO	European Society for Medical Oncology
FAD	final appraisal determination
FOLFIRINOX	oxaliplatin, plus irinotecan, plus calcium folinate plus fluorouracil
Gem	gemcitabine
Gem+Cap	gemcitabine plus capecitabine
GHS	global health status
H-H	cumulative hazard versus cumulative hazard
HR	hazard ratio
HRG	Healthcare Resource Group
HRQoL	health-related quality of life
ICER	incremental cost effectiveness ratio
ITT	intention-to-treat
IV	intravenous
IVRS	interactive voice recognition system
K-M	Kaplan-Meier
KPS	Karnofsky performance status
LCH	log-cumulative hazard
LCHP	log cumulative hazard plots
LY	life year
LYG	life years gained
MIMS	Monthly Index of Medical Specialities
Nab-Pac	nab-paclitaxel
Nab-Pac+Gem	nab-paclitaxel plus gemcitabine
NCCN	National Comprehensive Cancer Network
NICE	National Institute for Health and Care Excellence
NMA	network meta-analysis
NR	not reported

NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PAS	patient access scheme
PD	progressive disease
PFS	progression-free survival
PH	proportional hazards
PS	performance status
PSA	probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
Q	Quarter
Q-Q	quantile-quantile
QALY	quality adjusted life year
RCT	randomised controlled trial
RECIST	response evauation criteria in solid tumours
RR	relative risk
RRR	relative risk ratio
SA1	sensitivity analysis 1
SA2	sensitivity analysis 2
SA3	sensitivity analysis 3
SAE	serious adverse event
SAP	statistical analysis plan
SmPC	summary of product characteristics
SPARC	secreted protein acid and rich in cysteine
STA	single technology appraisal
TOT	time on treatment
TEAE	treatment-emergent adverse event
TRAE	treatment-related adverse event
TTP	time to progression
ULN	upper limit of normal
WTP	willingness to pay

1 SUMMARY

1.1 Scope of the submission

The remit of the Evidence Review Group (ERG) is to comment on the clinical and cost effectiveness evidence submitted to the National Institute for Health and Care Excellence (NICE) as part of the Single Technology Appraisal (STA) process. Clinical evidence and economic evidence have been submitted to NICE by Celgene Limited in support of the use of paclitaxel as albumin-bound nanoparticles (Abraxane®) with gemcitabine (Gem) for untreated metastatic adenocarcinoma of the pancreas. In this report, the formulation of paclitaxel as albumin-bound nanoparticles is referred to as Nab-Pac and the combination treatment is referred to as Nab-Pac+Gem.

Nab-Pac monotherapy is licensed in Europe as a second-line treatment for metastatic breast cancer and, in combination with carboplatin, for the first-line treatment of non-small cell lung cancer (NSCLC) in people whose disease is unsuitable for surgery or radiotherapy. On 2nd December 2013, the European Medicines Agency (EMA) approved an extension to the existing marketing authorisation allowing the use of Nab-Pac, co-administered with Gem, as a first-line treatment for people with metastatic adenocarcinoma of the pancreas.

The ERG notes that the appraisal under discussion in this report is an update of existing NICE guidance, TA360, published in October 2015. In TA360, NICE did not recommend the use of Nab-Pac+Gem as a treatment for previously untreated metastatic adenocarcinoma of the pancreas. The TA360 final appraisal determination (FAD) is available on the NICE website and a summary of the key points from the FAD and subsequent appeal is presented in Appendix 1 of this ERG report.

1.2 Critique of the decision problem in the company's submission

1.2.1 Population

The population described in the final scope issued by NICE is the same as the population recruited to the CA046 trial and discussed in the company submission (CS), i.e. patients with previously untreated metastatic adenocarcinoma of the pancreas.

Although 47% of all cases of pancreatic cancer are diagnosed in people aged ≥75 years, only 10% (n=84) of the patients recruited to the key trial (CA046) were aged ≥75 years. This means that the outcomes of the CA046 trial may not represent the outcomes of a substantial proportion of patients in the NHS who are diagnosed with metastatic adenocarcinoma pancreatic cancer.

In the European Public Assessment Report (EPAR) for Nab-Pac+Gem, the EMA cautions that there is no demonstrated benefit of treatment with Nab-Pac+Gem in people aged ≥75 years and that patients aged ≥75 years who were treated with Nab-Pac+Gem in the CA046 trial experienced more adverse events (AEs) and serious AEs (SAEs) than the overall trial population. The advice given in the Summary of Product Characteristics (SmPC) for Nab-Pac is that patients with pancreatic cancer who are aged ≥75 years should be carefully assessed for their ability to tolerate Nab-Pac+Gem, with special consideration given to performance status (PS), co-morbidities and increased risk of infection.

Clinical advice to the ERG is that most patients with metastatic adenocarcinoma of the pancreas who are seen by an oncologist are fit enough to be treated with Gem. Some patients are fit enough to tolerate a combination chemotherapy treatment (for example, gemcitabine plus capecitabine (Gem+Cap) or FOLFIRINOX). The company has not provided clear evidence to determine which patients are best suited to which of these treatments.

The company appears to consider that all patients who are fit enough to be treated with Gem, Gem+Cap or FOLFIRINOX are fit enough to be treated with Nab-Pac+Gem. However, the company considers that not all patients who are fit enough to tolerate treatment with Nab-Pac+Gem will be able to tolerate treatment with FOLFIRINOX. The ERG considers that the company has failed to clearly define the patient population for whom treatment with Nab-Pac+Gem is most appropriate.

1.2.2 Intervention

Nab-Pac was granted a UK marketing authorisation in 2013 for its use in combination with Gem for the first-line treatment of adult patients with metastatic adenocarcinoma of the pancreas. Hereafter referred to as Nab-Pac+Gem.

Nab-Paclitaxel is a formulation of paclitaxel in which paclitaxel is attached to nanoparticles of albumin and administered without the need for solvents. The company states that albumin-bound paclitaxel results in greater delivery of paclitaxel to the tumour site compared with conventional solvent-based paclitaxel formulations.

The treatment regimen for Nab-Pac+Gem is 125mg/m^2 intravenous (IV) infusion of Nab-Pac (over 30 minutes) immediately followed by Gem as a 1000mg/m^2 IV infusion (over 30 minutes) on Days 1, 8 and 15 of a 28-day cycle.

Nab-Pac+Gem is accepted for use in NHS Wales and NHS Scotland for the first-line treatment of adult patients with metastatic adenocarcinoma of the pancreas.

1.2.3 Comparators

The comparators specified in the final scope issued by NICE are Gem, Gem+Cap and a combination treatment consisting of four therapies known as FOLFIRINOX.

Gemcitabine

Direct clinical evidence is available for the comparison of the effectiveness of Nab-Pac+Gem versus Gem from the CA046 trial.

Gemcitabine+Capecitabine and FOLFIRINOX

In the absence of direct evidence for the comparison of Nab-Pac+Gem versus Gem+Cap or versus FOLFIRINOX, the company has conducted network meta-analyses (NMAs).

Gem+Cap and FOLFIRINOX are not licensed in the UK for the treatment of metastatic pancreatic cancer. As the components of both Gem+Cap and FOLFIRINOX are available as generics, there is no single company with an interest in supporting the use of either Gem+Cap or FOLFIRINOX. The use of Gem+Cap and FOLFIRINOX is not uniform across the NHS.

The company considers that Gem is the only valid comparator to Nab-Pac+Gem.

Outcomes

Direct evidence is available from the CA046 trial for the outcomes of overall survival (OS), progression-free survival (PFS), time to progression (TTP), objective response rate (ORR) and AEs. Health-related quality of life (HRQoL) data were not collected during the CA046 trial. In the clinical section of the CS, the company presents data from the SIEGE trial, collected using the European Organisation for Research and Treatment Cancer (EORTC) Quality of Life questionnaire (QLQ-C30). The SIEGE trial is an ongoing phase II study designed to explore different dosing schedules of Nab-Pac+Gem. Similar data are also presented from a US-based retrospective cross-sectional study of patients with metastatic pancreatic cancer that included patients treated with Nab-Pac+Gem, reported by Picozzi.

Other considerations

- An agreed patient access scheme (PAS) is in place for nab-paclitaxel
- The company has not identified any equality issues
- The company has presented a case for Nab-Pac+Gem to be assessed against the NICE End of Life criteria.

1.3 Summary of clinical effectiveness evidence submitted by the company

Results from the CA046 trial

The results of the most recent analysis of OS data from the CA046 trial (data cut-off: 9 May 2013) show that treatment with Nab-Pac+Gem statistically significantly improves median OS in comparison to treatment with Gem (8.7 months versus 6.6 months; hazard ratio [HR]=0.72, 95% confidence interval [CI]: 0.62 to 0.83) in patients with a Karnofsky PS (KPS) ≥70. Improvement in OS with Nab-Pac+Gem compared with Gem was generally consistent across patient baseline characteristics. At the time of the primary efficacy analysis, compared with treatment with Gem, treatment with Nab-Pac+Gem was shown, by independent review and by investigator assessment, to statistically significantly improve PFS.

The most common Grade 3 or 4 AEs associated with treatment with Nab-Pac+Gem were neutropenia, fatigue, metabolism and nutritional disorders, peripheral neuropathy, thrombocytopenia and anaemia. Although these AEs were also associated with treatment with Gem and Nab-Pac monotherapies, they occurred more frequently when patients were treated with Nab-Pac+Gem.

The company has presented early HRQoL results from the SIEGE trial within the clinical section of the CS. These data were collected using the EORTC QLQ-C30. The company reports that Global Health Scores (GHS) were generally stable throughout treatment; however, towards the end of the 6 treatment cycle period, data were difficult to interpret due to small patient numbers (n=22 in the concomitant Nab-Pac+Gem arm at Week 24).

In the absence of head-to-head clinical data that allow comparisons of the effectiveness of treatment with Nab-Pac+Gem versus Gem+Cap and versus FOLFIRINOX, the company performed NMAs. Despite the fact that a connected network could be formed by including only trials that compared treatments relevant to the decision problem, the company base case network included seven trials that provided evidence for treatments that were not listed in the final scope issued by NICE. However, the company performed a sensitivity analysis using a reduced network (fixed effects) that included only the comparators listed in the final scope issued by NICE and the ERG considers the results from this analysis more valid than the company's base case NMA results. In terms of OS, the results from this sensitivity analysis mirror the results from the base-case analysis and do not suggest a statistically significant treatment effect for Nab-Pac+Gem versus Gem+Cap (HR=1.10, 95% credible interval [CrI]: 0.67 to 1.84) or for Nab-Pac+Gem versus FOLFIRINOX (HR=0.77, 95% CrI:

0.58 to 1.01). The results from the company's base case NMA are used in the company's cost effectiveness model.

1.4 Summary of the ERG's critique of submitted clinical effectiveness evidence

The ERG considers that the CA046 trial was of good quality and well conducted. The trial data are mature and, with no patient crossover, the results allow for reasonable conclusions to be drawn regarding the clinical effectiveness of Nab-Pac+Gem versus Gem in the trial population. Substantial numbers of patients were recruited to the CA046 trial and patient baseline characteristics were balanced across both trial arms. The statistical methods used to analyse trial data were generally appropriate. Clinical advice to the ERG is that patients recruited to the trial were younger and fitter than the population of patients with metastatic disease treated in the NHS. Most notably, only 10% of the patients recruited to the trial were aged ≥75 years, whereas Cancer Research UK (CRUK) statistics suggest that almost half (47%) of all patients diagnosed with pancreatic cancer are in this age band. None of the participating treatment centres were based in the UK. The ERG considers that the absence of HRQoL data from patients in the CA046 trial is disappointing.

The ERG conducted assessments to determine the validity of the company's assumption that survival hazards are proportional over time. The ERG's analyses showed that, over time, the OS and PFS hazards from the two arms of the CA046 trial are not proportional. Consequently, all HRs results derived from the CA046 trial should be interpreted with caution. Furthermore, the ERG highlights that all of the company's NMA results (base case and sensitivity analyses) are affected by the lack of proportional hazards (PHs) in the CA046 trial and these results should also be interpreted with caution.

1.5 Summary of cost effectiveness evidence submitted by the company

For the comparison of treatment with Nab-Pac+Gem versus Gem, Kaplan-Meier (K-M) data from the CA046 trial were used as the basis for estimating patient survival. Stratified gamma curves were used to model OS, PFS and time on treatment (TOT). Resource use and costs were estimated based on information from the CA046 trial, published sources and advice from clinical experts. A Department of Health PAS discount was applied to the cost of Nab-Pac+Gem and full list prices were used to represent the cost of the comparator drugs.

The company's base case analysis prediction is a mean of 0.927 life years gained (LYG) for patients receiving Nab-Pac+Gem, 0.725 LYG for patients receiving Gem, 0.950 LYG for patients receiving Gem+Cap and 1.154 LYG for patients receiving FOLFIRINOX.

HRQoL data were not collected as part of the CA046 trial. Instead, the company adjusted the health state utility values reported by Romanus et al (2012) for use in a UK population. These adjusted values were used in the base case analysis for pre-progression (0.74) and progressive disease (0.67). The company used EQ-5D-5L data from the concomitant arm of the SIEGE trial (phase II, dose-scheduling trial of Nab-Pac+Gem) in separate scenario analyses.

The company submitted an updated model as part of the clarification response. The company's updated base case incremental cost effectiveness ratio (ICER) for the comparison of treatment with Nab-Pac+Gem versus Gem is £46,932 per quality adjusted life year (QALY) gained; treatment with Nab-Pac+Gem generates 0.144 additional QALYs at an additional cost of £6,755. For the comparison of treatment with Nab-Pac+Gem versus Gem+Cap and versus FOLFIRINOX, Nab-Pac+Gem is more costly and generates fewer QALYs.

For the comparison of treatment with Nab-Pac+Gem versus Gem, the company carried out a wide range of deterministic sensitivity analyses. The results show that the most influential parameter is the treatment variable used to parameterise OS. All of the other parameters that were varied had a lower impact on the size of the ICERs per QALY gained.

The results of the company's probabilistic sensitivity analysis show that Nab-Pac+Gem has a 64% probability of being cost effective compared to Gem at a willingness to pay threshold of £50,000 per QALY gained.

1.6 Summary of the ERG's critique of submitted cost effectiveness evidence

The company's model is generally well structured and correctly implemented. The ERG has corrected one error in the calculation of total LYs and QALYs. The three key issues that require exploration by the ERG in the company's model are: HRs used for treatment with Gem+Cap and with FOLFIRINOX, costing of drugs and modelling of TOT.

The company uses HRs from the NMA to estimate time-to-event outcomes for treatment with Gem+Cap and with FOLFIRINOX, which rely on the PH assumption holding for PFS and OS within the CA046 trial. Since PH has been shown not to hold for PFS or OS in the CA046 trial, using the results of the NMA in the model produces unreliable estimates for OS, PFS and TOT for treatment with Gem+Cap and with FOLFIRINOX. The ERG also has concerns about the company's use of HRs with a stratified Gamma model. The ERG has used published HRs for treatment with Gem+Cap versus Gem and with FOLFIRINOX versus Gem in the model to overcome the need for PH to hold in the CA046 trial; however, PH does not

hold in the ACCORD trial for either PFS or OS. Results for the comparison of treatment with Nab-Pac+Gem versus Gem+Cap and versus FOLFIRINOX should be treated with caution.

The company has estimated average treatment costs for the intervention and comparators using only a limited range of the vial sizes available to the NHS for each drug. By incorporating all available vial sizes in the calculation of drug costs, the ERG has decreased the average weekly cost of each first-line treatment in the company model.

The ERG advocates the use of K-M data directly as far as possible when time-to-event evidence comes from a single trial, and especially when the trial data are mature. The TOT data from the CA046 trial are complete and so represent the best possible evidence of time spent on treatment for the patients in that trial. However, the company has used a fully parametric model to estimate TOT, which introduces unnecessary uncertainties into the analysis and results in an overestimation of TOT for both treatments. The ERG has re-estimated TOT for treatment with Nab-Pac+Gem and with Gem using K-M data directly from the CA046 trial.

The company has also used parametric models to estimate PFS and OS for treatment with Nab-Pac+Gem and with Gem using mature data from the CA046 trial. The ERG investigated remodelling PFS and OS for treatment with Nab-Pac+Gem and with Gem using K-M data as far as possible then appending a parametric tail to extrapolate beyond the trial data. The ERG found that its re-modelling of PFS and OS for treatment with Nab-Pac+Gem and with Gem had only a small impact on the size of the ICERs per QALY gained.

Other issues identified by the ERG include the double counting of AE disutilities. The ERG has also provided two scenario analyses that investigate the impact of using different costs for some AEs and of using a different source of utility values.

1.7 Summary of company's case for End of Life criteria being met

The company has put forward a case that Nab-Pac+Gem meets NICE's End of Life criteria based on the following points:

- The company quotes data that show the median survival for patients with metastatic adenocarcinoma pancreatic cancer is less than 24 months
- Base case results generated by the company's economic model suggest that the mean difference in OS between patients treated with Nab-Pac+Gem versus Gem is 2.4 months
- When Nab-Pac+Gem is compared with Gem+Cap or FOLFIRINOX, the results from the company's base case NMA show that there is no statistically significant OS gain from Nab-Pac+Gem.

1.8 ERG commentary on End of Life criteria

The ERG agrees with the company that patients with metastatic adenocarcinoma of the pancreas have a life expectancy of less than 24 months.

An examination of the ERG's remodelled OS data suggests that treatment with Nab-Pac+Gem generates a mean survival gain of 2.44 months compared to Gem. When Nab-Pac+Gem is compared with Gem+Cap or FOLFIRINOX, the results from the company base case NMA show that there is no statistically significant OS gain from Nab-Pac+Gem.

1.9 ERG commentary on the robustness of evidence submitted by the company

1.9.1 Strengths

Clinical evidence

- The CA046 trial was of good quality, was well conducted and recruited 861 patients
- The trial data are mature and free from patient crossover
- To enable the comparison of Nab-Pac+Gem versus treatments listed in the final scope issued by NICE, the company carried out a range of NMAs
- The company fulfilled the ERG's clarification requests to a good standard.

Cost effectiveness evidence

- The economic model was well constructed
- The company carried out a comprehensive range of deterministic sensitivity and scenario analyses.

1.9.2 Weaknesses and areas of uncertainty

Clinical evidence

- The company is unable to define the characteristics of the patient population who would be most suited to treatment with Nab-Pac+Gem
- Patients aged ≥75 years make up almost half of all patients diagnosed with pancreatic cancer; however, only 10% of patients in the CA046 trial were aged ≥75 years
- The PFS and OS HRs from the CA046 trial data were calculated using a pre-specified method that relies on the assumption that hazards are proportional. However, as demonstrated by the company and the ERG, this assumption does not hold and therefore OS and PFS HRs must be interpreted with caution
- The lack of PH in the CA046 trial means that results from the company's NMAs should also be treated with caution.

Cost effectiveness evidence

- Time-to-event evidence for treatment with Nab-Pac+Gem versus Gem+Cap and versus FOLFIRINOX relies on results from the NMA, these results should be treated with caution due to the lack of PH in the CA046 trial
- Drug costs are not fully optimised, as the company calculated the cost of average doses based on a limited range of the vial sizes available to the NHS
- The company used parametric models to estimate time-to-event outcomes for treatment with Nab-Pac+Gem and Gem when data from the CA046 trial were mature or, in the case of TOT, complete and could be used directly in the model
- The model includes additional disutilities for AEs, which amounts to double counting because the base case utility values are derived from a trial and will already include any effect of AEs experienced by patients.

1.10 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG amended time-to-event estimates for all four first-line treatments in the company model. The ERG used published HRs from the Scheithauer and ACCORD trials to model OS, PFS and TOT for Gem+Cap versus Gem and FOLFIRINOX versus Gem respectively to overcome the issue of lack of PH in the CA046 trial. The PH assumption was found not to hold in the ACCORD trial, so results in the ERG's revised model for treatment with FOLFIRINOX should be treated with caution. The ERG's preferred method of modelling OS and PFS from the CA046 trial is to use K-M data for as long as possible, and then to append exponential curves to project outcomes for the remainder of the model time horizon. No projections were necessary for TOT, as data are complete in the CA046 trial.

The ERG re-estimated average weekly treatment costs for each of the four first-line treatments by taking into account all vial sizes for the constituent drugs for which prices are available. The ERG also removed added AE disutilities using a switch in the company model.

The ERG undertook two sensitivity analyses to investigate the impact of using amended AE resource-use costs and of using a different source of utility values.

1.11 Cost effectiveness conclusions

Application of the ERG model amendments in the base case results in an ICER for the comparison of Nab-Pac+Gem versus Gem of £41,250 per QALY gained. Application of the ERG's model amendments in the base case and all of the scenario analyses results in an ICER for the comparison of Nab-Pac+Gem versus Gem of £45,571 per QALY gained.

Application of the ERG model amendments results in an ICER for the comparison of Nab-Pac+Gem versus Gem+Cap of £99,837 per QALY gained. Application of the ERG's model amendments in the base case and all of the scenario analyses results in an ICER for the comparison of Nab-Pac+Gem versus Gem+Cap of £107,898 per QALY gained

Application of the ERG model amendments indicates that treatment with Nab-Pac+Gem is dominated by treatment with FOLFIRINOX. Application of the ERG's model amendments in the base case and all of the scenario analyses indicates that treatment with Nab-Pac+Gem is dominated by treatment with FOLFIRINOX.

2 BACKGROUND

2.1 Critique of company's description of underlying health problem

Section 3.1 of the company submission (CS) includes an overview of pancreatic cancer and Section 3.2 includes a description of the effects of metastatic pancreatic cancer on patients, carers and society. Section 3.4 includes UK epidemiology data for pancreatic cancer. Key points from these sections of the CS are included as bulleted items in Box 1 and Box 2. The Evidence Review Group (ERG) considers that these points are appropriate and relevant to the decision problem under consideration. The ERG notes that most (80 to 95%) pancreatic cancers are of adenocarcinoma histology.

Box 1 Company overview of pancreatic cancer

- Pancreatic cancers can form in either the exocrine or endocrine parenchyma, however, the vast majority start in the cells of the exocrine pancreas, with pancreatic adenocarcinoma accounting for approximately 80–95% of all pancreatic cancers.
- Most commonly, cancer originates in the head of the pancreas (approximately 75% of all cases), but it can also start in the body or tail. In the case of metastatic pancreatic adenocarcinoma, cancer originates in the pancreas but thereafter spreads to other areas of the body, with the most common sites of metastases being the liver, peritoneum, lungs and bones.
- Cases of pancreatic cancer in the UK are evenly split between males and females, but pancreatic cancer is more common in white and black people than in Asian people. In England, pancreatic cancer is also more common in people living in the most deprived areas. Approximately half (47%) of all pancreatic cancer cases are diagnosed in people aged ≥75 years, with cases in people under 40 years of age uncommon.
- There is no single known cause of pancreatic cancer, but there are a number of clinical, genetic and environmental risk factors, alongside the demographic factors, that increase the risk of pancreatic cancer. These include pancreatitis (chronic or hereditary), diabetes, mutation of the *BRCA* gene, obesity and smoking, and to a lesser extent previous cancer, hepatitis, Helicobacter pylori infection, alcohol and diet.
- Pancreatic cancer is an extremely aggressive and life-threatening malignancy. With mortality rates stabilising or increasing rather than declining, it is thought that pancreatic cancer may become the third leading cause of death from cancer in the European Union by 2025 (after lung and colorectal cancers).
- As the disease often remains asymptomatic at early stages, a high percentage of patients are diagnosed at an advanced stage. Only 30–40% of all patients present with disease confined to the pancreatic region and, in England, 79% of patients are diagnosed at Stage III or IV.
- Metastatic disease has a particularly poor prognosis, with median survival estimated at between 2 to 6 months; this depends on the size of the tumour and where it has spread. In addition to the extent of metastases, worse prognosis is also associated with poor performance status, pancreatic head tumour location, presence of biliary stent, and elevated levels of the CA19-9 antigen.
- In 2014, there were around 8,800 pancreatic cancer deaths in the UK (7,430 in England), which equates to 24 deaths every day, making it the fifth most common cause of cancer death. The latest incidence estimates for pancreatic cancer in the UK are based on 2013 data, when there were around 9,400 new cases (7,887 in England), which equates to 26 people diagnosed every day.

- Of people diagnosed with pancreatic cancer in England between 2005 and 2009, less than 20% survived beyond 12 months, and less than 4% survived to 5 years. Similar observations were made for people diagnosed between 2010 and 2011 in England and Wales.

Source: CS, Section 3.1 and Section 3.4

Box 2 Company overview of the effects of metastatic pancreatic cancer on patients, carers and society

- Patients with metastatic pancreatic cancer experience a variety of complications and disease-related symptoms, all of which affect normal living.

- Pancreatic cancer is typically symptomless in the early stages, but as it grows and spreads, symptoms can manifest (hence why most cases are diagnosed at an advanced stage). The exact symptoms a patient may experience will depend on the type of pancreatic cancer as well as its location. Common symptoms associated with adenocarcinoma include pancreatic insufficiency, weight loss, jaundice (head tumours) and abdominal/back pain (body-tail tumours). Patients with metastatic pancreatic adenocarcinoma may also experience additional symptoms associated with the site of metastases. For example, liver metastases can be associated with a swollen and painful abdomen, nausea, fatigue, and weight loss; while lung metastases can cause dyspnoea, persistent cough and chronic chest infections.

- We might expect patients with pancreatic cancer to experience some detrimental impact on quality of life as a result of their disease, and there are some reports of reduced quality of life in the literature; particularly with regard to mental health that appears to worsen with advanced disease, likely as a result of their poor prognosis. However, formal assessment of health-related quality of life resulting in a single health index (utility), shows a similar index score between patients with advanced pancreatic cancer who are receiving active treatment (gemcitabine) and the general population.

- For patients who are actively employed, the cost of productivity loss has been estimated to be as high as €87,205 (approximately £74,228). Given the poor prognosis of patients with metastatic pancreatic adenocarcinoma, there is also a societal burden of disease due to premature mortality. In Europe, the cost to society of premature death due to pancreatic cancer is estimated at €3.9 billion (approximately £3.3 billion).

Source: CS, Section 3.2

2.2 Company's overview of current service provision

The company presents an overview of the clinical care pathway in Section 3.3 of the CS. The ERG considers the company's overview to be relevant to the decision problem under consideration. The company discusses the use of three treatments for metastatic pancreatic cancer in the NHS in England: i) gemcitabine monotherapy (Gem); ii) gemcitabine+capecitabine (Gem+Cap); iii) a combination treatment of oxaliplatin, irinotecan, calcium folinate and flurouracil known as FOLFIRINOX. Details of the three treatments are summarised in Table 1.

The company reports that treatment options differ between NHS England, NHS Wales[1] and NHS Scotland[2] as nab-paclitaxel combined with gemcitabine (Nab-Pac+Gem) is currently available as a treatment option for patients with metastatic pancreatic cancer in both NHS Wales and NHS Scotland.

Table 1 Summary of company overview of current service provision

Treatment	Licensed in Europe	NICE guidance	Treatment regimen	Available uniformly across NHS?	Available as a generic product?
Gem	Yes	TA25[3] (2001)	IV 1000mg/m^2 (30 min). Weekly for 7 weeks followed by a week of rest. Thereafter once a week on a 3-weekly cycle	Yes	Yes
Gem+Cap	No	N/A	Gem IV 1000mg/m^2 (30 min) once a week on a 3-weekly cycle. Capecitabine tablets 1666mg/m^2 daily on a 3-weekly cycle	No	Yes
FOLFIRINOX	No	N/A	Oxaliplatin, irinotecan, leucovorin and flurouracil (5-FU) administered via central line, Portacath or PICC line. • Oxaliplatin 85mg/m^2 (2 hrs) • Leucovorin 400mg/m^2 (2 hrs) • Irinotecan 180mg/m^2 (90 min) • 5-FU 400mg/m^2 administered by IV bolus, then as a continuous IV infusion of 2400mg/m^2 over 46 hrs every 2 weeks	No. Modified treatment regimens are used in some centres	Yes

5-FU= flurouracil; IV=intravenous; PICC=peripherally inserted central catheter
Source: CS, Section 3.3

Gemcitabine monotherapy

The company states (CS, p34) that in NICE guidance published in 2001 (TA25[3]), Gem is recommended as a first-line treatment for people with advanced or metastatic pancreatic cancer if they have a Karnofsky Performance Status (KPS) of 50 or more. The ERG agrees with the company that gemcitabine remains the only treatment currently recommended by NICE for metastatic pancreatic cancer.

Gemcitabine+capecitabine

The company reports (CS, p35) that Gem+Cap is not a licensed treatment regimen for metastatic pancreatic cancer and, as generic versions of gemcitabine and capecitabine are available, there is no single company with a commercial interest in promoting or supporting the use of this regimen.

Clinical advice to the company (CS, p35), and to the ERG, is that there is modest use of Gem+Cap in the NHS. The company's market research data (CS, p35 and Section 2.4 of this ERG report) suggest that [redacted] of patients with metastatic pancreatic adenocarcinoma who receive treatment in the NHS are likely to receive Gem+Cap. Clinical advice to the ERG is that in the NHS, no more than [redacted] of patients are treated with Gem+Cap.

The company has reservations about the clinical effectiveness of treatment with Gem+Cap compared with the effectiveness of treatment with Gem (CS, p42). The company states that

there are three publications[4-6] that report the results of randomised controlled trials (RCTs) comparing Gem+Cap versus Gem in patients with advanced or metastatic pancreatic cancer; however, none of the three trials[4-6] has demonstrated evidence of a significant overall survival (OS) benefit from treatment with Gem+Cap compared with Gem. The company observes (CS, p42) that a 2009 meta-analysis (Cunningham[4]) of data from the three published trials[4-6] 'attempts' to demonstrate that there is a statistically significant OS benefit associated with treatment with Gem+Cap when compared with Gem even though no OS benefit was reported in the individual trials. The ERG notes that the results of the published meta-analysis[4] demonstrated a significant OS gain for Gem+Cap when compared with Gem (hazard ratio [HR]=0.86; 95% confidence interval [CI]: 0.75 to 0.98; p=0.02) in a mixed group of patients with locally advanced or metastatic disease. The company reports (CS, p43) that the results of the meta-analysis[4] were '*not that well received in clinical circles*.'

FOLFIRINOX

The ERG agrees with the company (CS, p34) that FOLFIRINOX is not licensed in Europe for the treatment of patients with metastatic pancreatic adenocarcinoma. Furthermore, as generic versions of all the components of FOLFIRINOX are available, there is no single company with a commercial interest in promoting or supporting the use of this regimen.

The ERG agrees with the company (CS, p41) that FOLFIRINOX is an intensive therapy that requires the use of chemotherapy port and infusion pump management services. The ERG is aware that the standard regimen of FOLFIRINOX for the treatment of metastatic pancreatic cancer, as described in Table 1, was established in the trial by Conroy.[7] In this trial,[7] median OS for patients treated with FOLFIRINOX was 11.1 months compared with 6.8 months for patients treated with Gem (HR=0.57; 95% CI: 0.45 to 0.73).

The company describes two main issues relevant to the use of FOLFIRINOX and these are set out in Box 3.

Box 3 Company identified issues with the use of FOLFIRINOX in the NHS

1. The use of FOLFIRINOX is not uniform across the NHS, mainly because there is no organisational infrastructure to support treatment administration and to manage the adverse events (AEs) associated with FOLFIRINOX.

2. A modified FOLFIRINOX regimen is given in some treatment centres to try to reduce the toxicity and the burden of administration; however, there is no randomised clinical trial evidence to support the clinical effectiveness of any modified version of FOLFIRINOX.

Source: CS, p42

The company states (Box 3, point 1) that FOLFIRINOX is not used uniformly across the NHS because of the lack of infrastructure to support treatment administration and manage the

associated AEs. Clinical advice to the ERG is that treatment centres that support the use of Nab-Pac+Gem also have the infrastructure to support the use of FOLFIRINOX.

The ERG agrees with the company's statements describing the availability and modification of FOLFIRINOX in UK clinical practice. However, clinical advice to the ERG is that there is no RCT evidence to support the dose reductions and dose omissions that are commonly required when treating patients with Nab-Pac+Gem. The ERG notes from the professional organisation submission to NICE[8] that patients seen at peripheral chemotherapy units who are eligible for treatment with FOLFIRINOX travel to specialist cancer centres to receive the treatment. Clinical advice to the ERG is that patients who are suitable for treatment with Nab-Pac+Gem will also be treated at specialist cancer centres.

The company states that FOLFIRINOX is offered to patients who are aged ≤70 years, have an Eastern Co-operative Group (ECOG) performance status (PS) of 0 or 1 and have very minor co-morbidities. Data from the company's market research (CS, p35 and Section 2.4 of this ERG report) suggest that, in the UK, between [redacted] of patients with metastatic pancreatic adenocarcinoma who receive treatment in the NHS are treated with FOLFIRINOX. Clinical advice to the ERG is that the use of FOLFIRINOX in the NHS may be limited by the toxicity of this treatment regimen which can only be offered to patients with PS of 0 or 1 with limited co-morbidities.

2.3 Place of Nab-Pac+Gem in the treatment pathway

The company describes Nab-Pac (CS, p19) as '…an innovative formulation of paclitaxel that facilitates selective and efficient accumulation of active treatment to promote cell death at the tumour site.' The company reports that the treatment effects of Nab-Pac are enhanced by the concomitant use of Gem.

It is specified in the Summary of Product Characteristics (SmPC[9]) for Nab-Pac that treatment is administered as a 125mg/m^2 IV infusion (over 30 minutes on Days 1, 8 and 15 of a 28-day cycle. Gem is administered as a 1000mg/m^2 IV infusion over 30 minutes immediately after Nab-Pac (CS, p19).

The company is clear that Gem is the only valid comparator to Nab-Pac+Gem in the first-line setting for patients with metastatic pancreatic cancer. The company states that the introduction of Nab-Pac+Gem into the NHS will only have an impact on the current NHS usage of Gem and will not affect the current NHS usage of either Gem+Cap or FOLFIRINOX. The company's rationale for this position on FOLFIRINOX (CS, p34-35) is set out in Box 4.

Box 4 Company's rationale for the place of Nab-Pac+Gem in the treatment pathway

- FOLFIRINOX treatment is intensive and only suitable for use in a subgroup of patients and, that the subgroup of patients who are suitable for treatment with FOLFIRINOX are easily identified in clinical practice
- Patients who are suitable for treatment with FOLFIRINOX are clinically distinct from patients who are treated with Gem but who could be treated with Nab-Pac+Gem
- Patients suitable for treatment with Nab-Pac+Gem are easily identified and are clinically distinct from patients who are suitable for treatment with Gem or with FOLFIRINOX

Source: CS, p34-35

Clinical advice to the ERG is that patients in the NHS who are better suited to treatment with FOLFIRINOX are easily identified from patients who are better suited to treatment with Gem. However, the distinction between patients who are better suited to treatment with FOLFIRINOX and patients who might be better suited to treatment with Nab-Pac+Gem is not clear, and it is difficult to formulate guidance for patient selection. The ERG notes that there is no known biomarker or patient characteristic that can be used to predict response to treatment with either Nab-Pac+Gem or FOLFIRINOX.[10]

The company's proposed use of Nab-Pac+Gem relative to other treatments is described in Table 2. The company's position is based on clinical expert advice given to the company. The ERG notes from Table 2 that the company claims that Nab-Pac+Gem can be used in patients of any age, including patients aged ≥75 years. The ERG questions the evidence supporting this claim (see Section 3.1 of this ERG report) and notes that the advice given in Section 4.4 of the SmPC[9] for Nab-Pac is that there is no demonstrated treatment benefit of Nab-Pac+Gem compared with Gem for patients with pancreatic cancer who are aged ≥75 years. The SmPC[9] for Nab-Pac includes the caution that patients who are ≥75 years should be carefully assessed for their ability to tolerate Nab-Pac+Gem, with special consideration given to PS, co-morbidities and increased risk of infection.

The company does not consider the use of Gem+Cap to be a standard of care in the NHS and does not fully discuss the characteristics of patients who are likely to receive treatment with Gem+Cap, except to say that these patients will continue to be offered treatment with Gem+Cap even if Nab-Pac+Gem becomes available for use in the NHS. Clinical advice to the ERG is that Gem+Cap is not commonly used to treat patients in the NHS. It may be used in patients with bulky symptomatic disease who are not fit for treatment with FOLFIRINOX.

Table 2 Proposed place of Nab-Pac+Gem in the treatment pathway with ERG comment

Treatment	Company proposed patient population	ERG comment
FOLFIRINOX	≤70 years ECOG PS 0 or 1 Minor co-morbidities (e.g. well controlled hypertension)	Clinical advice to the ERG is that in the NHS, FOLFIRINOX is used in patients who are ≥70 years if they have a PS of 0 or 1 and are aware of the potential side effects The company's market research shows that in the UK [redacted] of patients are treated with FOLFIRINOX
Gem	Any age ECOG PS ≥2	Agree
Nab-Pac+Gem	Any age (use in people aged over 80 years is supported by real-world evidence). ECOG PS 0 or 1 FOLFIRINOX treatment not suitable	The ERG notes that the SmPC for Nab-Pac includes a caution advising that there is no evidence of clinical efficacy of Nab-Pac+Gem in patients ≥75 years and that patients with pancreatic cancer who are aged ≥75 years should be carefully assessed for their ability to tolerate Nab-Pac+Gem with special consideration to performance status, co-morbidities and increased risk of infections. The company has not defined the patient population not suitable for treatment with FOLFIRINOX
Gem+Cap	Not discussed	Not in common usage in the NHS. May be used to treat patients with bulky symptomatic disease who are not fit enough for treatment with FOLFIRINOX The company's market research shows that in the UK [redacted] of patients are treated with Gem+Cap

ECOG=Eastern Co-operative Oncology Group; PS=performance status
Source: CS, p34-35

The ERG notes that the baseline characteristics of the patient populations recruited to the key trials of Nab-Pac+Gem (CA046[11,12]) and FOLFIRINOX (Conroy[7]) are very similar (Table 3). The ERG also notes that median OS for patients treated with Gem in the CA046 and Conroy trials is comparable (6.8 months and 6.6 months, respectively), underlining the similarities between the trial cohorts and the difficulty in distinguishing between patients in the NHS who are suited to treatment with FOLFIRINOX and Nab-Pac+Gem. Clinical advice to the ERG is that many of the patients recruited to the CA046 trial would have been suitable for treatment with FOLFIRINOX.

Table 3 Comparison of patient populations in the CA046 trial and in the Conroy 2011 trial

Characteristic	CA046 Nab-Pac+Gem vs Gem N=861 n (%)	Conroy 2011 FOLFIRINOX vs Gem N=342 n (%)	
Median age (years)	63	61	
Male	502 (58)	105 (61)	
Performance status			
KPS		**ECOG**	
100	138/858 (16)	0	65 (38)
90	378/858 (44)	1	106 (62)
80	277/858 (32)	2	1 (0)
70	63/858 (7)		
60	2/858 (<1)		
Tumour location			
Head	371 (43)	65 (38)	
Body	268 (31)	56 (32)	
Tail	215 (25)	45 (26)	
Unknown	4 (1)	NR	
Multicentric	NR	6 (3)	
Number of metastatic sites n%			
1	54 (6)		
2	408 (47)	Median of 2 (range 1 to 6)	
3	276 (32)		
>3	123 (14)		

ECOG=Eastern Cooperative Oncology Group; KPS=Karnofsky performance status; NR=not reported
Source: CS, Table 11 and Conroy 2011 Table 1

The ERG notes that guidelines[13] published by the European Society for Medical Oncology (ESMO) provide advice for the use of Nab-Pac+Gem and FOLFIRINOX in the treatment of metastatic pancreatic cancer. In these guidelines[13] the ESMO Committee states that there are no data to support the use of Nab-Pac+Gem over FOLFIRINOX. The Committee considered that either FOLFIRINOX or Nab-Pac+Gem could be offered to patients who have serum bilirubin levels of less than 1.5 times the upper limit of normal and are of good PS (ECOG 0 or 1). The ESMO guidelines[13] also include the statement that treatment with Nab-Pac+Gem could be considered to treat 'very selected patients' with ECOG PS 2.

In the 2014 ERG report for TA360,[14] it was noted that the company was unable to identify a single 'optimal' subgroup of patients who were suitable for treatment with Nab-Pac+Gem and the ERG considers that the company has yet to clearly identify this 'optimal' subgroup.

2.4 Impact of Nab-Pac+Gem on the use of Gem, Gem+Cap and FOLFIRINOX in the NHS

To support the claim that, in NHS clinical practice, the use of Nab-Pac+Gem will only have an impact on the use of Gem (CS, p35-37), the company has provided the results of market research conducted by Kantar.[15]

The company describes the research[15] as being based on an audit of Europe and UK patient chart data. The ERG understands that the data were derived from [redacted]. The company was unable to supply the source file for the market research when requested by the ERG (via the clarification process); the ERG is, therefore, unable to comment on the validity of the research, or to verify the results. However, the ERG notes that the presented data summarise the first-line treatments administered during each quarter (Q) of the audit year and the proportions of patients who received them. Data from the UK (Q2 2015 and Q4 2015) are shown in Table 4. The company states that during the 2015 data collection period, Nab-Pac+Gem was available via the Cancer Drugs Fund (CDF) in England and was recommended for use in Scotland in February 2015 and in Wales in October 2015.

The company reports that, in Q4, there was a [redacted] increase in the number of patients treated with Nab-Pac+Gem compared with the number treated in Q2. The company highlights that this increase coincided with an [redacted] decrease in patients treated with Gem. The use of FOLFIRINOX and Gem doublet (likely to be Gem+Cap) remained constant between Q2 and Q4.

The ERG notes that data presented by the company (CS, Figure 2) indicate an increasing trend towards the use of FOLFIRINOX in Europe between Q4 in 2014 and Q4 in 2015 [redacted]. The trend in the European data could suggest that the use of FOLFIRINOX in the UK might have also increased during 2015 (given the increasing experience of clinicians with administering FOLFIRINOX) and that the plateau in the usage of FOLFIRINOX in the UK may reflect some displacement by the use of Nab-Pac+Gem. The ERG also notes that the company did not provide any demographic information that would enable any comparison to be made between the patients who were treated with Nab-Pac+Gem and patients who were treated with FOLFIRINOX during 2015.

Table 4 Company market research data for first-line treatment of metastatic pancreatic adenocarcinoma in the UK

[redacted]	[redacted]	
	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Q=quarter
*Note that the sum of each column is not 100% as the full audit includes other treatments not relevant to the present appraisal
Source: CS, Figure 2

2.5 Life expectancy

The company describes the life expectancy of people diagnosed with pancreatic cancer in Section 3.4 of the CS. The company presents information published by CRUK[16] that shows that pancreatic cancer was the fifth most common cause of cancer deaths in the UK in 2014 (approximately 8,800 deaths in the UK and 7,430 deaths in England). The company also presents the 12-month and 5-year survival data from CRUK for the years 2005 to 2009 (people in England) and 2010 to 2011 (people in England and Wales).[16] The company observes (CS, p38) that, in the absence of new treatments, the (low) current survival rates are likely to remain unchanged (Table 5). The company's observation is supported by details on the CRUK[16] website that highlight that, in the UK, survival from pancreatic cancer '…has not shown much improvement in the last 40 years.'

Table 5 12-month and 5-year survival rates in pancreatic cancer

Year	12-month survival rate	5-year survival rate
2005 – 2009 (England[16])	<20%	4%
2010 – 2011 (England and Wales[16])	21%	3%

Source: CS, p38

2.6 Summary of relevant clinical guidance and guidelines

The company provides details of relevant published guidance and treatment guidelines in Section 3.5 of the CS. These are reproduced in Table 6. The company observes that NICE expects to publish a guideline[17] specific to pancreatic cancer in January 2018.

Table 6 Company summary of guidance and guidelines relevant to metastatic pancreatic cancer

Organisation Year	Title	Summary
NICE guidance		
TA25[3] (2001)	Guidance on the use of gemcitabine for the treatment of pancreatic cancer	• People with advanced or metastatic adenocarcinoma of the pancreas may be treated with Gem as a first-line treatment if they have KPS ≥50 • Gem should not be used for people with pancreatic cancer who are suitable for surgery that may cure their cancer, or those who have KPS <50 • Gem should not be used as a second-line treatment for people with pancreatic cancer, because there is insufficient evidence to support this practice
International clinical guidelines		
European Society for Medical Oncology[13] (2015)	Cancer of the pancreas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up	The following treatment options should be considered for the treatment of patients with metastatic pancreatic cancer according to their general status: • If the ECOG PS of the patient is 0 or 1 and the bilirubin level is below 1.5 x ULN, two types of combination chemotherapy: the FOLFIRINOX regimen or the combination of Nab-Pac+Gem should be considered • For patients with ECOG PS of 2 and/or bilirubin level higher than 1.5 x ULN, monotherapy with Gem could be considered • In very selected patients with ECOG PS 2 due to heavy tumour load, Nab-Pac+Gem can be considered for best chance of response • For patients with ECOG PS of 3/4 with significant morbidities and very short life-expectancy, only symptomatic treatment can be considered
American Society of Clinical Oncology[18] (2016)	Metastatic Pancreatic Cancer: American Society of Clinical Oncology Clinical Practice Guideline	Key treatment recommendations for first-line therapy: • FOLFIRINOX is recommended for patients who meet all the following criteria: ECOG PS 0/1, favourable comorbidity profile, patient preference and support system for aggressive medical therapy, and access to chemotherapy port and infusion pump management services • Nab-Pac+Gem is recommended for patients who meet all the following criteria: ECOG PS 0/1, relatively favourable comorbidity profile, patient preference and support system for relatively aggressive medical therapy • Gem alone is recommended for patients who have either an ECOG PS 2 or a comorbidity profile that precludes more-aggressive regimens and who wish to pursue cancer-directed therapy. The addition of either capecitabine or erlotinib to gemcitabine may be offered in this setting • Patients with an ECOG PS ≥3 or with poorly controlled comorbid conditions despite ongoing active medical care should be offered cancer-directed therapy only on a case-by-case basis. The major emphasis should be on optimising supportive care measures

National Comprehensive Cancer Network[19] (2016)	NCCN Practice Guidelines in Oncology: Pancreatic Adenocarcinoma. Version 2. 2016	Preferred first-line therapy for patients with good PS (defined as ECOG PS 0/1 with good pain management, patent biliary stent, and adequate nutritional intake): • Clinical trial • FOLFIRINOX • Nab-Pac+Gem FOLFIRINOX should be limited to patients with ECOG PS 0/1; Nab-Pac+Gem is reasonable for patients with KPS ≥70 Options for patients with good PS: • Gemcitabine plus erlotinib • Gemcitabine-based combination therapy • Gemcitabine monotherapy • Capecitabine or continuous infusion 5-FU • Fluoropyrimidine plus oxaliplatin First-line therapy options for patients with poor PS: • Gemcitabine • Palliative and best supportive care

5-FU=fluorouracil; ECOG=Eastern Co-operative Oncology Group; KPS=Karnofsky Performance Status; PS=Performance Status; ULN=upper limit of normal
Source: CS, Table 5

2.7 Innovation

The company puts forward the case that Nab-Pac+Gem is an innovative treatment (CS, Section 2.5). The company's case is set out in Box 5.

Box 5 Company's case that Nab-Pac+Gem is an innovative treatment

- Metastatic pancreatic cancer has an extremely poor prognosis, with median survival estimated at between 2 to 6 months. The development of new treatments has been very limited in recent years, and despite numerous clinical trials, there has only been a modest improvement in life expectancy

- Gem-based therapy has been the standard of care for the first-line treatment of patients with unresectable locally advanced and/or metastatic pancreatic cancer since 1997 and is still the only single agent licensed in Europe. Its use is associated with a median survival of 5 to 7 months[10]

- In a phase II/III trial[7,14] not designed for registration, a significant survival benefit for patients with metastatic pancreatic cancer was observed with the combination regimen FOLFIRINOX compared with gemcitabine monotherapy (11.1 months vs 6.8 months); however, this regimen has often been found to be poorly tolerated, except by very fit patients, and modified versions with unproven efficacy in the context of a randomised controlled phase III clinical trial are often adopted in clinical practice in an attempt to improve tolerability of the regimen

- There is clearly a high level of unmet need associated with metastatic pancreatic cancer. This was previously acknowledged by NICE, who recognised that current treatments are limited in efficacy or associated with significant AEs such that additional treatment options in this area would be of value

- In the pivotal, regulatory phase III trial, CA046, Nab-Pac+Gem became the first chemotherapy doublet to demonstrate both a statistically significant and clinically meaningful survival benefit (defined as 6 to 8 weeks by people affected by pancreatic cancer over established standard of care (Gem). While some additive toxicity was observed (as expected a priori), the Nab-Pac+Gem regimen was generally well tolerated, with the majority of AEs potentially manageable through dose modification

- While the health-related benefits to patients should be captured in the QALY, the fact that

Nab-Pac+Gem offers a licensed treatment option with an innovative mechanism of action proven to improve life expectancy for patients with metastatic adenocarcinoma of the pancreas should be considered a 'step-change' in the management of this condition with extremely high unmet need

- The more emotional aspects of an extension to life and the benefit of a life-extending medicine to the family and friends of a patient with a life-threatening malignancy should be considered, and these will not be captured in the QALY. These benefits were recognised by Pancreatic Cancer UK[20] as part of their Two More Months campaign, launched in February 2014 in an attempt to ensure Nab-Pac+Gem was available for use via the NHS across the UK. This campaign illustrates how access to Nab-Pac+Gem could give metastatic adenocarcinoma of the pancreas patients and their families the ability to achieve particular personal ambitions at the end of their life.

QALY=quality adjusted life year
Source: CS, p30-31

Clinical advice to the ERG is that treatment with Nab-Pac+Gem and FOLFIRINOX are associated with more AEs than treatment with Gem. Nab-Pac+Gem and FOLFIRINOX have similar AE profiles and both treatment regimens require dose reductions and modifications in managing the AEs.

2.8 Number of patients eligible for treatment with Nab-Pac+Gem

The company estimates that in England, the maximum number of patients who will be eligible for treatment with Nab-Pac+Gem is 3147 each year. The company's method for calculating this number is presented in Table 7 along with the ERG's estimate. The ERG estimate is based on the 2014 incidence rate of pancreatic cancer published by CRUK. The ERG considers that the company's estimate of 3147 is reasonable.

Table 7 Company estimate of numbers of patients eligible for treatment

	Number of patients	
Parameter	**Company estimate**	**ERG estimate**
Incidence of pancreatic cancer in England in 2013	7887[16]	8080[16]
Cases of pancreatic cancer that are adenocarcinoma = 80-95%[13,21]	7492	7676
Cases that are metastatic disease = 60-70%[13]	5245	5373
Patients suitable for chemotherapy = 50-60%*	3147	3224

ERG=Evidence Review Group
*Expert opinion to the company
Source: CS, Section 3.4

3 CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

A summary of the ERG's comparison of the decision problem outlined in the final scope issued by NICE[22] and that addressed within the CS is presented in Table 8. Each parameter in Table 8 is discussed in more detail in the text following the table (Section 3.1 to Section 3.6).

Table 8 Comparison between NICE scope and company decision problem

Final scope issued by NICE Parameter and specification	**Summary of a comparison between the decision problem stated in the NICE scope and addressed in the CS**
Population People with previously untreated metastatic adenocarcinoma of the pancreas	People with previously untreated metastatic adenocarcinoma of the pancreas
Intervention Paclitaxel as albumin-bound nanoparticles (Nab-Pac)	Nab-Pac+Gem (as specified in its marketing authorisation)
Comparators Gem Gem+Cap FOLFIRINOX	**Direct evidence** Nab-Pac+Gem versus Gem The CA046 trial was designed to compare the clinical effectiveness of Nab-Pac+Gem versus Gem **Indirect evidence** Nab-Pac+Gem versus Gem+Cap Nab-Pac+Gem versus FOLFIRINOX The company has carried out NMAs to compare the relative effectiveness of treatment with Nab-Pac+Gem versus Gem+Cap and versus FOLFIRINOX. However, the company states (CS, p34-35) that only Gem is a relevant comparator to Nab-Pac+Gem

Final scope issued by NICE Parameter and specification	Summary of a comparison between the decision problem stated in the NICE scope and addressed in the CS
Outcomes OS PFS RR AEs HRQoL	The company has presented results for all the outcomes detailed in the final scope issued by NICE
Economic analysis The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per QALY	Cost effectiveness has been assessed using ICERs per QALY gained
If appropriate, the appraisal should include consideration of the costs and implications of additional testing for biological markers, but will not make recommendations on specific diagnostic tests or devices	Not applicable – the anticipated marketing authorisation for Nab-Pac+Gem is the whole population of patients with metastatic adenocarcinoma of the pancreas
The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared	The model time horizon is 10 years
Costs will be considered from an NHS and Personal Social Services perspective	Costs have been considered from an NHS perspective
The availability of any patient access schemes (PAS) for the intervention or comparator technologies will be taken into account	Details relating to the PAS for Nab-Pac+Gem have been provided in a confidential appendix that form part of the CS
Subgroups to be considered None specified	None identified
Special considerations None identified	None identified

AE=adverse effects of treatment; CS=company submission; ERG=evidence review group; HRQoL=health-related quality of life; ICER=incremental cost effectiveness ratio; ITT=intention to treat; NICE=National Institute for Health and Care Excellence; NMA=network meta-analysis; OS=overall survival; PAS=patient access scheme; PFS=progression-free survival; QALY=quality adjusted life year; RR=response rate
Source: CS, pp17-18

3.1 Population

The population described in the final scope issued by NICE is people with previously untreated metastatic adenocarcinoma of the pancreas. The population discussed in the CS is the population recruited to the CA046 trial, which is identical to the population described in the final scope issued by NICE.

Use of nab-paclitaxel+ gemcitabine in patients aged ≥75 years

The company reports (CS, p32) that 47% of all cases of pancreatic cancer are diagnosed in people aged ≥75 years. These data are derived from figures available on the CRUK

website.[16] The ERG notes that only 10% (n=84) of the patients recruited to the CA046 trial were ≥75 years. The ERG is concerned that the outcomes of the CA046 trial may not represent the outcomes of a substantial proportion of patients in the NHS who are diagnosed with pancreatic cancer, i.e. patients aged ≥75 years.

The company discusses the consideration given to patients aged ≥75 years in the EPAR[9] and the SmPC[9] for Nab-Pac (CS, p27). In the EPAR,[9] it is stated that for people aged ≥75 years there is no demonstrated treatment benefit of Nab-Pac+Gem compared with Gem. The ERG notes that the results of a pre-specified subgroup analysis of OS for patients aged ≥75 years in the CA046 trial showed a poorer OS outcome for patients treated with Nab-Pac+Gem compared with treatment with Gem (HR=1.08; 95% CI: 0.65 to 1.80).

In the SmPC,[9] the European Medicines Agency (EMA) also cautions that patients aged ≥75 years who were treated with Nab-Pac+Gem in the CA046 trial experienced more adverse events (AEs) and serious adverse events (SAEs) than the overall trial population. The AEs and SAEs included haematological toxicities, peripheral neuropathy, decreased appetite and dehydration. The advice given in the SmPC[9] is that patients with pancreatic cancer who are aged ≥75 years should be carefully assessed for their ability to tolerate Nab-Pac+Gem, with special consideration given to PS, co-morbidities and increased risk of infection.

The company states (CS, p26) that the advice given in the SmPC[9] is based on a small number of patients. The company also reports (CS, p117) that data from a retrospective analysis[23] of Italian patients with advanced pancreatic cancer treated with Nab-Pac+Gem show that similar rates of Grade 3 and Grade 4 AEs were recorded for patients aged <75 years (n=176) and those aged ≥75 years (n=32). The ERG notes that the study[23] was based on data from clinical records, included patients with advanced pancreatic cancer and included only 32 patients aged ≥75 years.

Clinical advice to the company (CS, p113) is that, in NHS clinical practice, age would not be a barrier to treatment with Nab-Pac+Gem. The clinical experts advised the company (CS, p113) that they would consider patients aged ≥75 for treatment with Nab-Pac+Gem.

3.2 Intervention

The intervention specified in the final scope issued by NICE is Nab-Pac. The intervention discussed in the CS is Nab-Pac+Gem; this is appropriate and reflects the marketing authorisation[9] issued by the EMA on 20th December 2013. The licensed indication for Nab-Pac+Gem is for the first-line treatment of adults with metastatic adenocarcinoma of the pancreas.

Nab-Pac is administered intravenously over 30 minutes at a dose of 125mg/m^2 on days 1, 8 and 15 of each 28-day cycle. Gem is administered intravenously over 30 minutes at a dose of 1000mg/m^2. Gem is administered immediately after the administration of Nab-Pac has been completed.

The company states (CS, p24) that paclitaxel prevents the growth of cancer cells by obstructing cell division and fostering cell death. Paclitaxel is used to treat other types of cancer, including breast and lung cancer. The company describes Nab-Pac as a novel formulation of paclitaxel in which paclitaxel is attached to nanoparticles of albumin and administered without the need for solvents. Albumin-bound paclitaxel results in greater delivery of paclitaxel to the tumour site compared with conventional solvent-based paclitaxel formulations. The company reports that, when combined with Gem, a '…novel, synergistic effect' results in an increase in, and the stabilisation of, levels of intra-tumoural Gem.[24]

Nab-Pac+Gem in the UK

In the Final Appraisal Determination (FAD) for TA360[25] issued in October 2015, NICE did not recommend the use of Nab-Pac+Gem for patients in the NHS with previously untreated metastatic pancreatic cancer. The company reports (CS, p27) that Nab-Pac+Gem was available to patients via CDF between March 2014 and November 2015, and was then removed from the CDF '…in preparation for the new approach to the appraisal and funding of cancer drugs in England'. The ERG notes that Nab-Pac was one of 17 drugs removed from the CDF in November 2015 as a result of a review by a partnership between NHS England, NICE, Public Health England and the Department of Health.[26]

Nab-Pac+Gem is available for use in NHS Wales[1] and in NHS Scotland.[2]

Other licensed indications for nab-paclitaxel

Nab-Pac monotherapy is licensed in Europe[9] for the treatment of people with metastatic breast cancer whose disease has progressed following first-line treatment and who are unsuitable for treatments containing anthracyclines. Nab-Pac in combination with carboplatin is licensed in Europe[9] for the first-line treatment of NSCLC in people whose disease is unsuitable for surgery or radiotherapy. NICE has not appraised Nab-Pac for use in either of these licensed indications.

3.3 Comparators

The comparators specified in the final scope issued by NICE are Gem, Gem+Cap and FOLFIRINOX.

3.3.1 Included comparators

Gemcitabine

Direct clinical evidence is available for the comparison of the effectiveness of Nab-Pac+Gem versus Gem from the CA046 trial. Throughout the CS (pp14, 15, 20, 23, 34, 35, 38, 142, 248), the company is clear that it considers Gem to be the only relevant comparator to treatment with Nab-Pac+Gem.

Gem+Cap and FOLFIRINOX

In the absence of any direct evidence to allow the effectiveness of Nab-Pac+Gem to be compared with that of Gem+Cap or FOLFIRINOX, the company has conducted network meta-analyses (NMAs). However, the company states that the results of the comparative clinical effectiveness and cost effectiveness analyses of Nab-Pac+Gem versus Gem+Cap and versus FOLFIRINOX are only presented in the CS for completeness. The ERG (and the company) consider that the results of the company's NMA should be treated with caution.

The company does not consider either Gem+Cap or FOLFIRINOX to be relevant comparators to Nab-Pac+Gem for the reasons described in Sections 2.2 and 2.3 of this ERG report.

The company contends that the limited use of Gem+Cap in the NHS means that it does not represent standard of care and that the current use of Gem+Cap in the NHS would not be displaced if Nab-Pac+Gem became available for use. The ERG notes that data presented by the company (CS, Figure 2) indicate that, in 2015, [redacted] of treated patients received Gem+Cap.

The company also contends that patients in the NHS who are suitable for treatment with Nab-Pac+Gem are easily identified and are clinically distinct from patients who would be considered suitable for treatment with Gem or with FOLFIRINOX. Clinical advice to the ERG is that patients who are suitable for treatment with FOLFIRINOX are clinically distinct from patients who are suitable for treatment with Gem monotherapy. However, the ERG is uncertain that patients with metastatic pancreatic cancer who may be considered suitable for treatment with Nab-Pac+Gem in the NHS are clinically distinct from patients who would currently be treated with FOLFIRINOX. Clinical advice to the ERG is that it would be difficult to clearly establish which patients in the NHS would better suited to treatment with Nab-Pac+Gem rather than with FOLFIRINOX.

3.4 Outcomes

The outcomes specified in the final scope issued by NICE are: OS, progression-free survival (PFS), time to tumour progression (TTP), objective response rate (ORR), AEs and health-related quality of life (HRQoL). Direct evidence for the effectiveness of Nab-Pac+Gem versus Gem is derived from the CA046 trial and details relating to OS, PFS, TTP, ORR (reported as overall response rate and disease control rate) and AEs associated with these two treatments are presented in the CS.

No HRQoL data were collected as part of the CA046 trial; the company has used EQ-5D[27] data from the SIEGE trial[28] to populate the economic model. The SIEGE trial[28] is a phase II randomised trial designed to compare two different treatment schedules of Nab-Pac+Gem; the trial does not provide a comparison of Nab-Pac+Gem with Gem. In the clinical section of the CS, (CS, p70-71) the company briefly discusses HRQoL data (EORTC QLQ-C30[29]) from LAPACT,[30] an ongoing phase II single arm trial of patients with locally advanced pancreatic cancer who were treated with Nab-Pac+Gem. The company also summarises HRQoL (EORTC QLQ-C30[29] and EORTC QLQ-PAN26)[31] results from a cross-sectional study[32] of patients with metastatic pancreatic cancer in the US who were treated with three cycles of Nab-Pac+Gem compared with patients who were newly diagnosed.

As specified in the final scope issued by NICE, the cost effectiveness of treatments was expressed in terms of the incremental cost per quality adjusted life year (QALY) gained and outcomes were assessed over a 10-year time period (equivalent to a lifetime horizon). Costs were considered from an NHS perspective.

3.5 Subgroups

No patient subgroups were identified in the final scope issued by NICE. In the CS, the company has presented results from the CA046 trial for subgroups based on prognostic factors that were pre-specified in the trial protocol. These were age, sex, PS, tumour location, liver metastases, number of metastatic sites, level of CA19-9 and region of patient recruitment.

3.6 Other relevant factors

The company has not identified any equity or equality issues. Details relating to the patient access scheme (PAS) for Nab-Pac have been provided by the company in a confidential appendix that formed part of the CS.

4 CLINICAL EFFECTIVENESS SYSTEMATIC REVIEW METHODS

4.1 Systematic review methods

The company carried out a systematic search of the literature in May 2013 and updates were conducted in March 2014 and July 2016 to identify phase II-IV RCTs, systematic reviews and meta-analyses designed to investigate the efficacy and safety of pharmacological interventions for people with previously untreated metastatic adenocarcinoma of the pancreas. In addition to the electronic database searches, a number of conference proceedings were searched. The company states that hand searches of the reference lists of the systematic reviews and meta-analyses identified during the searches were performed to identify studies that were potentially relevant to the research question.

The data sources searched, and the time spans for the searches, are provided in Table 9 and a summary of, and ERG comments on, the review methods used by the company are presented in Table 10.

Table 9 Data sources for the clinical systematic review

Search strategy component	Source	Search date range	
		Start	End
Electronic database searches	EMBASE	1974	13 July 2016
	MEDLINE	1946	
	MEDLINE In-Process	1946	
	Cochrane Central Library of Controlled Trials (CENTRAL)	1996	13 July 2016
	Cochrane Database of Systematic Reviews (CDSR)		
	Database of Abstracts of Reviews of Effectiveness (DARE)	1995	13 July 2016
	Database of Health Technology Assessments (HTA)	1995	13 July 2016
	Cumulative Index to Nursing and Allied Health (CINAHL)	1981	24 July 2016
Congress proceedings	American Society of Clinical Oncology (ASCO) ASCO Gastrointestinal Cancers Symposium (GICS or ASCO GI) European Society for Medical Oncology (ESMO) ESMO World Congress on Gastrointestinal Cancer (World GI)	2012	Between 16-17 August 2016

Source: CS, pp44-45

Table 10 Summary of, and ERG comment on, the systematic review methods used by the company

Review method	Results	ERG comment
Searching		
Sources searched: • Electronic databases • Congress proceedings • Clinical trial registries	Initial search=4943 Update 03/2014=635 Update 07/2016=1227	• The last update was carried out in July 2016, meaning that there is a risk that some relevant studies may not have been included in the search results • It is unclear whether the time-periods for the update searches overlapped. Not including an overlap may result in some relevant studies being missed • Only CENTRAL was searched for ongoing trials. Any clinical trials that are only registered in other databases (e.g. ClinicalTrials.gov) will have been missed
Formal eligibility criteria		
Two analysts independently assessed study eligibility based on: - the primary eligibility criteria presented in Table 3, Appendix 2 of the CS (p15)	Unique studies Initial search=97 Update 03/2014=6 Update 07/2016=18	• Use of two independent assessors improves the quality of reviews
Additional eligibility criteria		
The company states that a narrower scope was employed following confirmation of the indication for Nab-Pac+Gem leading to changes in the following: • Population – changed from people with previously untreated metastatic adenocarcinoma of the pancreas to APC patients, of whom at least 50% patients with metastatic pancreatic cancer and must not have had prior systemic therapy for metastatic disease • Comparators - specific Gem-based chemotherapy combinations and FOLFIRINOX, rather than the less-defined list of comparators specified at the primary stage The secondary eligibility criteria are presented in Table 7 of the CS (p46)	Unique studies Initial search=16 Update 03/2014=0 Update 07/2016=1	• Only studies meeting the additional eligibility criteria were included and summarised in the CS
Quality assessment		
The company assessed the risk of bias of the CA046 trial using the minimum criteria recommended by NICE[33] The results of the assessment of risk of bias of the RCTs included in the company's NMA are presented in Appendix 4 of the CS		

APC=advanced pancreatic cancer; CS=company submission; ERG=Evidence Review Group; NMA=network meta-analysis; NICE=National Institute for Health and Care Excellence; RCT=randomised controlled trial
Source: CS, p44-49 and p62-63

4.1.1 Evidence synthesis

The company presents direct evidence to support the clinical efficacy of Nab-Pac+Gem from one RCT (the CA046 trial). The CS includes a narrative description of this trial. No evidence synthesis was undertaken.

4.2 ERG critique of direct clinical effectiveness evidence

4.2.1 Identified trials

Key trial: the CA046 trial

The company presents evidence for the clinical effectiveness of Nab-Pac+Gem from the CA046 trial (also known as mPACT). The CA046 trial was an open-label, multicentre, phase III RCT that was designed to investigate the efficacy and safety of Nab-Pac+Gem versus Gem in patients with untreated metastatic adenocarcinoma of the pancreas. Patients were randomised to receive either Nab-Pac+Gem (Nab-Pac at 125mg/m^2 and Gem at 1000mg/m^2) or Gem 1000mg/m^2. Treatment in both arms was given on days 1, 8 ,15, 29, 36 and 43 for the first 56 days (Cycle 1) and then on days 1, 8 and 15 of a 28-day cycle. Details relevant to the CA046 trial are reported in the CS, in the trial clinical study report (CSR[11]) and in a published paper.[12]

Other trials

Neither the company nor the ERG identified any other trials that directly compare Nab-Pac+Gem with any of the comparators listed in the final scope issued by NICE.

4.2.2 Key characteristics of the CA046 trial

The key characteristics of the CA046 trial are provided in the CS (CS, p50-59) and are summarised in Table 11.

The trial was conducted internationally, however, none of the treatment centres were located in the UK. Clinical advice to the ERG is that treatment centres based in Western Europe and Australia would be most like NHS treatment centres. Patients were randomised to receive either Nab-Pac+Gem (n=431) or Gem (n=430) using a centralised interactive voice recognition system (IVRS). Randomisation was stratified by geographic region (North America versus other), baseline KPS (70 to 80 versus 90 to 100) and presence or absence of liver metastases.

The ERG considers that the CA046 trial was well designed and well conducted. Substantial numbers of patients were recruited; patient crossover did not take place and the trial data are mature. These attributes mean that it is possible to draw reasonable conclusions about the clinical effectiveness of Nab-Pac+Gem versus Gem in the trial population.

Table 11 Key characteristics of the CA046 trial

Location	International, multicentre study involving 151 centres in the USA (n=68), Australia (n=20), Russian Federation (n=19), Italy (n=12), Canada (n=7), Ukraine (n=7), Spain (n=7),

	Germany (n=4), Austria (n=3), France (n=2) and Belgium (n=2).
Design	Randomised, open-label, phase III Stratification factors: geographic region (North America vs other), KPS (70 to 80 vs 90 to 100), presence of liver metastases (yes or no)
Patient eligibility criteria	Inclusion criteria • Metastatic adenocarcinoma of the pancreas (histologically or cytologically confirmed) • Initial diagnosis of metastatic disease ≤6 weeks prior to randomisation • One or more metastatic tumours measurable by CT scan • No previous treatment of metastatic disease • Men or women (nonpregnant and nonlactating), age ≥18 years • Baseline blood counts (see Table 9 of the CS for details) • Baseline chemistry (see Table 9 of the CS for details) • Acceptable coagulation studies • KPS ≥70. Exclusion criteria • Patients with islet cell neoplasms • Known brain metastases unless treated and well controlled for at least 3 months • Only locally advanced disease • Coumadin use • Known infection with HIV, hepatitis B, or hepatitis C • Active, uncontrolled infection(s) requiring systemic therapy • Major surgery ≤4 weeks prior to Day 1 of treatment • History of allergy or hypersensitivity to the study drug • Serious medical risk factors involving any of the major organ systems • History of malignancy in the last 5 years • History of connective tissue disorders • History of interstitial lung disease, slowly progressive dyspnoea and unproductive cough, sarcoidosis, silicosis, idiopathic pulmonary fibrosis, pulmonary hypersensitivity pneumonitis or multiple allergies; • History of chronic leukaemias • High cardiovascular risk • History of peripheral artery disease
Duration of study	Enrolment: May 2009 to March 2011 Primary analysis: 17th Sept 2012 (data cut-off) Follow-up analysis: 9th May 2013 (data cut-off) Death rate at final analysis: 90%

Intervention(s) and comparator(s)	**Nab-Pac+Gem** (n=431): 30 to 40 minute IV infusion of Nab-Pac (125mg/m^2) followed by a 30 to 40 minute IV infusion of Gem (1,000 mg/m^2) on Days 1, 8, 15, 29, 36 and 43 of a 56-day cycle in Cycle 1 only and on Days 1, 8 and 15 of a 28-day cycle in Cycle 2 and onward **Gem** (n=430): 30 to 40 minute IV infusion of Gem (1,000 mg/m^2) on Days 1, 8, 15, 29, 36 and 43 of a 56-day cycle in Cycle 1 only and on Days 1, 8 and 15 of a 28-day cycle in Cycle 2 and onward Treatment was continued until progressive disease or unacceptable toxicity. Dose modifications including a maximum of two dose reductions were allowed from the original dose for toxicity management
Primary outcome	OS (time from randomisation to death from any cause)
Secondary outcomes	PFS, objective tumour response, safety, tolerability
Other efficacy outcomes	PFS and ORR by investigator assessment, time to response and response duration, disease control rate, time to treatment failure, changes in serum CA19-9, tumour response based on PET scans
Duration of follow-up	Median follow-up at the primary analysis (17 September 2012) was 9.1 months (range, 0.1–36.9) in the Nab-Pac+Gem arm, and 7.4 months (range, 0.0–31.3) in the Gem arm

CS=company submission; CT=computed tomography; HIV=human immunodeficiency virus; IV=intravenous; KPS=Karnofsky performance score; ORR=objective response rate; OS=overall survival; PET=positron emission tomography; PFS=progression-free survival; vs=versus
Source: CS, Table 9

4.2.3 Characteristics of patients enrolled in the CA046 trial

The key baseline characteristics of patients included in the CA046 trial are listed in Table 12. The company reports (CS, p60) that the patients' baseline characteristics were well balanced between trial arms. The company is confident (and the ERG agrees) that the population of patients recruited to the CA046 trial matches the patient population identified in the final scope issued by NICE, whilst acknowledging that the patient population in the trial is younger and fitter than patients treated in the NHS.

The ERG notes from the CS (p32) that approximately half (47%) of all pancreatic cancer cases are diagnosed in people aged ≥75 years; however, the company reports (CS, p27) that only 10% of patients in the CA046 trial were aged 75 years or over. Clinical advice to the ERG is that in the NHS, almost half of patients diagnosed with pancreatic cancer are aged ≥75 years. In the SmPC[9] for Nab-Pac, the EMA cautions that there is a lack of evidence of clinical efficacy in people aged ≥75 years and that patients aged ≥75 years who were treated with Nab-Pac+Gem in the CA046 trial experienced more AEs and SAEs than the overall trial population. Consequently, it is not known if the treatment effect estimated for the population of the CA046 trial is generalisable to the population expected to be seen in clinical practice. Furthermore, the occurrence of AEs and SAEs that would be seen in clinical practice may be underestimated by the CA046 trial, due to the small proportion of people aged ≥75 years in the trial population.

Table 12 Key characteristics of patients in the CA046 trial

Characteristic		Nab-Pac+Gem N=431	Gem N=430	All N=861
Age (median) years (range)		62 (27 to 86)	63 (32 to 88)	63 (27 to 88)
Age categories	< 65 –n (%)	254 (59)	242 (56)	496 (58)
	≥ 65 –n (%)	177 (41)	188 (44)	365 (42)
Sex n (%)	Female	186 (43)	173 (40)	359 (42)
	Male	245 (57)	257 (60)	502 (58)
Race or ethnic group n (%)	Asian	8 (2)	9 (2)	17 (2)
	Black	16 (4)	16 (4)	32 (4)
	White	378 (88)	375 (87)	753 (87)
	Hispanic	25 (6)	26 (6)	26 (6)
	Other	4 (1)	4 (1)	8 (1)
Region n (%)	Australia	61 (14)	59 (14)	120 (14)
	Eastern Europe	64 (15)	62 (14)	126 (15)
	North America	268 (62)	271 (63)	539 (63)
	Western Europe	38 (9)	38 (9)	76 (9)
KPS score n/total n (%)	100	69/429 (16)	69/429 (16)	138/858 (16)
	90	179/429 (42)	199/429 (46)	378/858 (44)
	80	149/429 (35)	128/429 (30)	277/858 (32)
	70	30/429 (7)	33/429 (8)	63/858 (7)
	60	2/429 (<1)	0/429	2/858 (<1)
Pancreatic tumour location n (%)	Head	191 (44)	180 (42)	371 (43)
	Body	132 (31)	136 (32)	268 (31)
	Tail	105 (24)	110 (26)	215 (25)
	Unknown	3 (1)	4 (1)	7 (1)
Site of metastatic disease n (%)	Liver	365 (85)	360 (84)	725 (84)
	Lung	153 (35)	184 (43)	337 (39)
	Peritoneum	19 (4)	10 (2)	29 (3)
Number of metastatic sites n (%)	1	33 (8)	21 (5)	54 (6)
	2	202 (47)	206 (48)	408 (47)
	3	136 (32)	140 (33)	276 (32)
	>3	60 (14)	63 (15)	123 (14)
Previous therapy n (%)	Radiation therapy	19 (4)	11 (3)	30 (3)
	Chemotherapy	23 (5)	12 (3)	35 (4)
	Whipple procedure	32 (7)	30 (7)	62 (7)
	Biliary stent	80 (19)	68 (16)	148 (17)

KPS=Karnofsky performance status
Source: CS, Table 11

4.2.4 Statistical approach adopted

Information relevant to the statistical approach taken by the company to analyse data from the CA046 trial has been taken from the CS, the trial CSR, the trial protocol,[34] and the statistical analysis plan (SAP).[35]

Sample size calculation

Details of the sample size calculation performed by the company are reported in the CS (p56). The trial was powered (at the 90% level) to detect a HR for death, for the comparison of the effectiveness of Nab-Pac+Gem versus Gem, of 0.769 with a two-sided alpha level of 0.049. This required a sample size of 842, with 608 events. The ERG is satisfied that the company's pre-specified sample size calculation was carried out correctly.

Protocol amendments

A list of protocol amendments is included in the CSR (p58-62). The key protocol amendments that could have influenced the outcomes and analyses of CA046 are:

Protocol amendment 1 (20 Mar 2009)

- Added serum CA19-9 and plasma secreted protein acid and rich in cysteine (SPARC) levels as secondary objectives and endpoints
- Added an interim analysis (evaluated by independent data monitoring committee) with the possibility of stopping the study prematurely due to lack of efficacy
- Clarified the primary efficacy endpoint hypotheses and modified the confidence interval (CI) of the OS HR to account for the interim efficacy analysis

Protocol amendment 2 (17 Nov 2009)

- Added language to the randomisation stratification categories
- Modified the statistical procedure for testing the secondary efficacy endpoints from the Hochberg[36] procedure to a sequential step-down procedure, where PFS was tested first and ORR was tested only if PFS was statistically significant

Protocol amendment 4 (30 Sep 2010)

- Modified sample size (increased required number of deaths to at least 608, and enrolled patients to 842) to allow for an increase in statistical power from 80% to 90%

The ERG notes that the protocol amendment changes took place before any data analyses. Thus, they were not driven by the results of the trial and, therefore, are unlikely to be a cause for concern.

Outcomes and analyses

The intention-to-treat (ITT) population, which consisted of all randomised patients, was used in all efficacy analyses. Safety analyses were carried out in the treated population, which consisted of all randomised patients who received at least one dose of the trial drug.

The primary outcome of OS was analysed using the Kaplan-Meier (K-M) method, and a stratified log-rank test. A stratified Cox proportional hazards (PH) model was used to estimate the HR and corresponding 95% CI. Cox regression analyses, including adjustments for stratification factors, were also carried out to estimate treatment effects.

The secondary outcomes were PFS and ORR, which were assessed by independent review according to Response Evaluation in Solid Tumours (RECIST) criteria, and safety and tolerability of the administered treatments. Investigator-assessed PFS and ORR were also reported. Cox PH methods and a stratified log-rank test were used to generate PFS results. Patient ORRs were compared between the two arms of the trial using the chi-square test.

The ERG is satisfied that all outcomes were pre-specified in the SAP and reported in full in the CSR.

The analyses carried out by the company to generate OS and PFS HRs from CA046 trial data were conducted using Cox PH modelling. The validity of this method relies on the survival hazards of patients in the two arms of the trial being proportional over time. The company assessed the validity of the PH assumption using the following methods:

- Visual inspection of log-cumulative hazard (LCH) plots
- Visual inspection of Schoenfeld residual plots and corresponding correlation estimates and p-values assessing proportionality
- Comparison of observed and predicted K-M curves (estimated using a Cox PH regression model)

The company presents each of these plots for the outcomes of OS and PFS in Appendix 4 of the CS. However, in their interpretation of these plots (CS, p98-101), the company does not draw any firm conclusions about whether OS and PFS hazards for patients in the two arms of the CA046 trial can be considered to be proportional over time.

The ERG has assessed the validity of the OS and PFS PH assumptions by plotting the cumulative hazard associated with Nab-Pac+Gem treatment versus the cumulative hazard associated with Gem treatment (H-H plot) for each outcome, together with the constant PH trend line. If the PH assumption is valid for these data, the data points should lie close to the trend line and be evenly distributed either side of it. Figure 1 displays the H-H plot for the OS

data. The plot suggests that the PH assumption for OS data is violated; data points fall below the PH trend line in the first half of the analysis and then sit above the trend line in the second half. The violation is confirmed by a regression test of linearity, the result from which indicates statistically significant non-linearity (p<0.001).

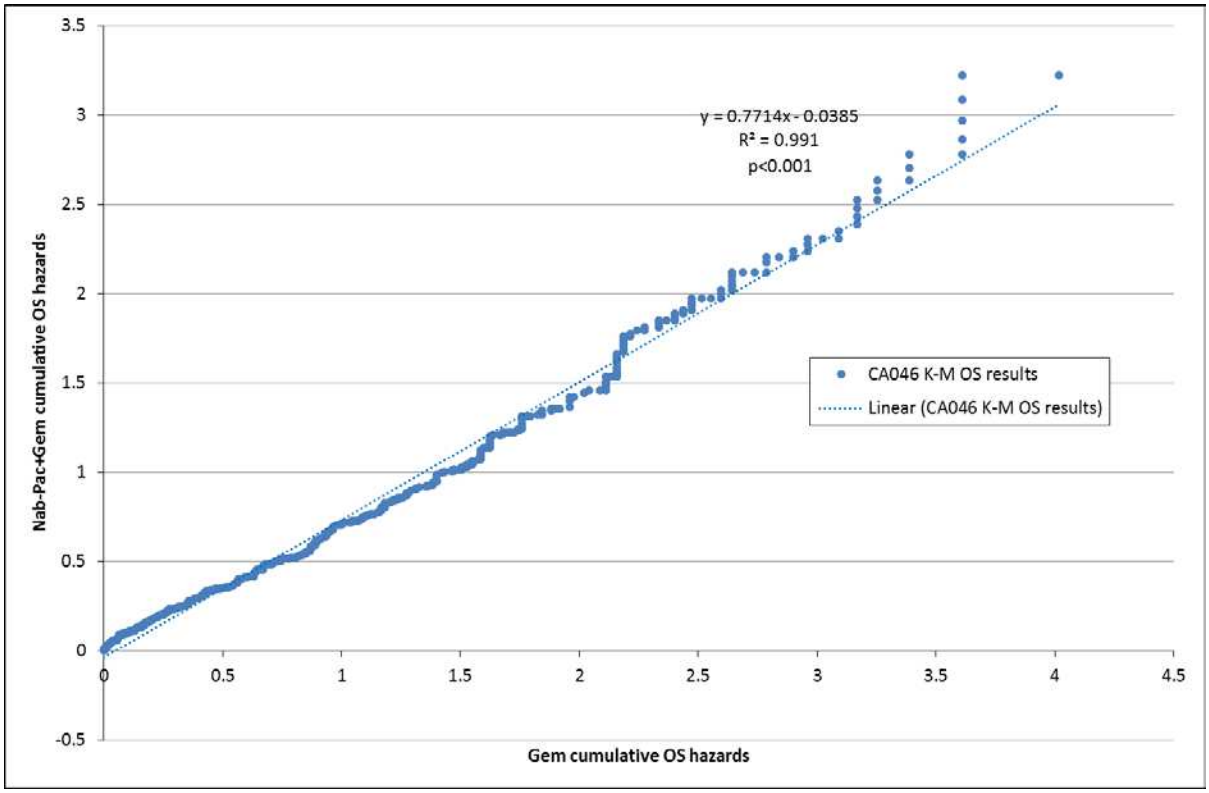

Figure 1 ERG comparative cumulative OS hazard plot for Nab-Pac+Gem vs Gem in CA046 trial

OS=overall survival

The H-H plot for PFS data (Figure 2) shows a systematic divergence from the PH trend line, suggesting that the PH assumption is violated. The violation is confirmed by a regression test of linearity, the result from which indicates statistically significant non-linearity (p<0.001).

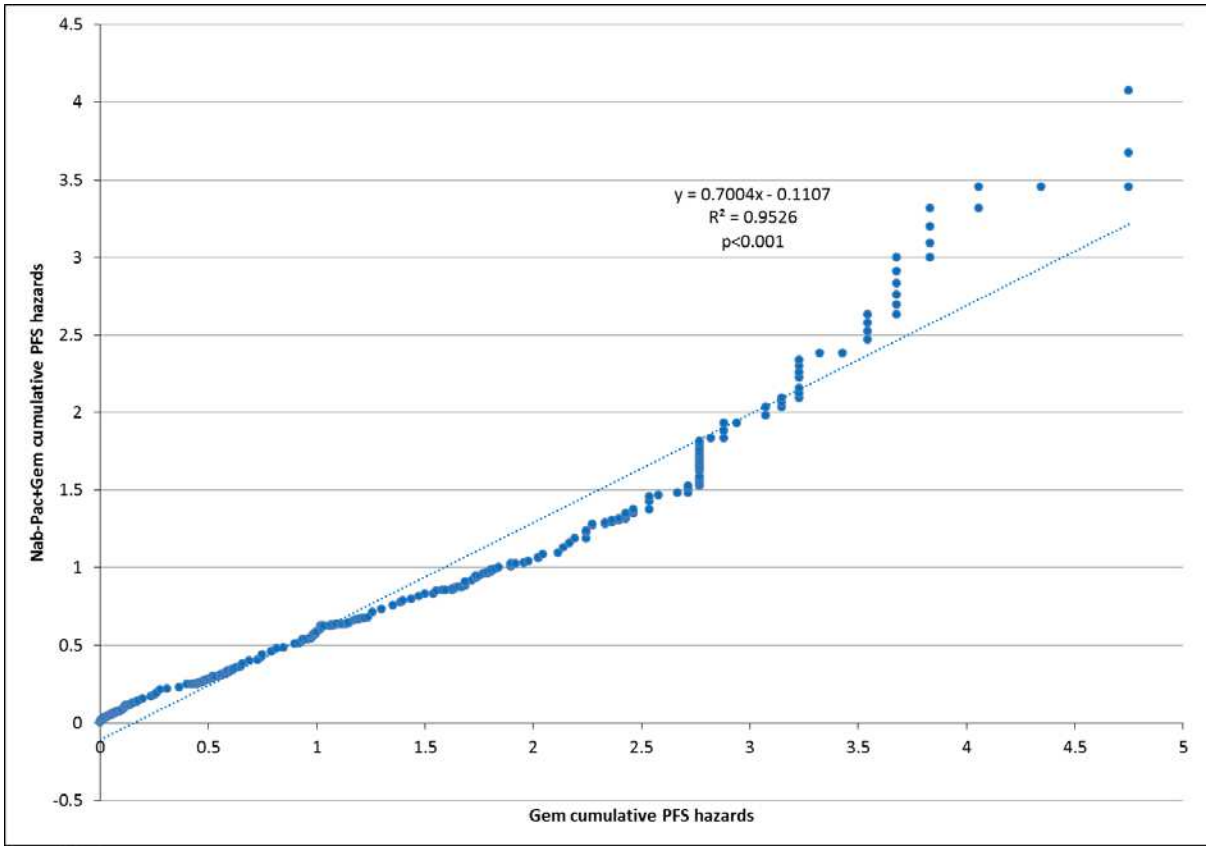

Figure 2 Comparative cumulative PFS hazard plot for Nab-Pac+Gem vs Gem in CA046 trial

PFS=progression-free survival

The ERG's H-H plots suggest that the PH assumption does not hold for the CA046 trial OS or PFS data and, consequently, HRs are not an appropriate summary of treatment effect for this trial. It is not possible to know whether the reported HRs would overestimate or underestimate the effect of Nab-Pac+Gem in comparison to Gem, and all CA046 trial HRs should be interpreted with caution.

Subgroup analyses

Subgroup analyses for the primary outcome of OS were pre-specified in the SAP. The ERG is satisfied that the results from these analyses are provided in full in the CSR. It is stated in the CS (p55) that, for the subgroup analyses of geographic region, baseline KPS, and presence of liver metastases, clinical data rather than randomisation data were used (i.e., analyses were based on data in the clinical report file collected and verified on site rather than on the IVRS information provided for randomisation). The company explained in their response to the ERG clarification letter that the clinical data were source document verified whilst the randomisation data were not and, therefore, the clinical data were considered to be the more accurate. The ERG is satisfied with the company's explanation.

Sensitivity analyses

Sensitivity analyses to investigate the robustness of the results of the primary outcome analyses were pre-specified in the SAP. The ERG is satisfied that the results of all of the sensitivity analyses were fully reported in the CSR.

Timing of analyses

An interim analysis for OS was pre-specified in the CA046 trial protocol. This was performed after at least 200 patients had been followed for at least 6 months from the date of randomisation. The interim analysis was designed to evaluate futility, with the possibility of stopping the trial early due to lack of efficacy. As determined by the pre-specified sample size calculation, the final analysis of OS was conducted when at least 608 deaths had occurred; all deaths that occurred on, or prior to, the projected clinical cut-off date, were included in the analysis.

The final OS analysis was based on 692 deaths (80% of patients, data cut-off: 17 September 2012). Median follow-up was 9.1 months in the Nab-Pac+Gem arm and 7.4 months in the Gem arm.

An updated analysis of OS from the CA046 trial with an extended data cut-off (8 months longer than the final OS analysis) was reported in a paper by Goldstein[37] (data cut-off: 9 May 2013). At the time of the updated analysis, 774 (90%) patients in the ITT population had died and median follow-up was 13.9 months. The ERG is aware that this is a post-hoc analysis; however, this is not a cause for concern as it is unlikely that the updated results could be subject to bias. The motivation for undertaking the follow-up analysis is clear - at this point, 90% of the ITT population had experienced an event compared with 80% at the time of the primary analysis.

Overall, the ERG considers that appropriate statistical methods were used for the analyses of CA046 trial data, with the exception of the inappropriate generation of HRs to compare survival (OS and PFS) between trial arms.

4.2.5 Risk of bias assessment for the CA042 trial

The company assessed the risk of bias in the CA046 trial using the minimum criteria set out in NICE's Guide to the Methods of Technology Appraisal.[33] The ERG agrees with the company that the risk of bias is low for all the criteria listed in Table 13. The ERG notes that the CA046 trial was of an open-label design; however, a blinded review of the investigator-assessed radiological outcomes was conducted. The ERG considers that a notable strength of the CA046 trial is that the study protocol prohibited treatment crossover.

Table 13 Risk of bias assessment of the CA046 trial

Study question	Company assessment		
	Addressed in the trial?	Risk of bias	ERG comment
Was randomisation carried out appropriately?	Yes. Randomisation schedule was generated by a randomisation statistician, with stratification for key prognostic factors.	Low	Agree
Was the concealment of treatment allocation adequate?	Yes. Randomisation was implemented via a centralised IVRS.	Low	Agree
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes. Patient demographics were well balanced, with no key differences between treatment groups.	Low	Agree
Were the care providers, participants and outcome assessors blind to treatment allocation?	Independent assessors were blinded; care providers and participants were not.	Low	Agree
Were there any unexpected imbalances in drop-outs between groups?	No. The most common reason for study withdrawal in both treatment arms was disease progression, which is fully accounted for within efficacy assessments.	Low	Agree
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No.	Low	Agree
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes. Efficacy analyses were performed according to the ITT principle, with standard censoring methods used to account for missing data.	Low	Agree

IVRS=interactive voice response system; ITT=intention-to-treat
Source: CS, Table 12

4.2.6 Participant disposition in the CA046 trial

The company provided a Consolidated Standards of Reporting Trials (CONSORT) flow chart to show patient disposition in the CA046 at the time of the final analysis (CS, Figure 3). In summary:

- in total, 861 patients were randomised; 420 were treated with Nab-Pac+Gem, and 403 were treated with Gem
- over 90% of patients in both treatment arms had discontinued therapy at the time of the final analysis data cut-off; the majority due to progressive disease (47% in the Nab-Pac+Gem arm and 61% in the Gem arm)
- one patient was randomised to treatment with Gem but received treatment with Nab-Pac+Gem

- at the time of final analysis, median duration of treatment was 3.9 months (range: 0.1–21.9) in the Nab-Pac+Gem arm and 2.8 months (range: 0.1–21.5) in the Gem arm
- in the Nab-Pac+Gem arm, 41% of patients had reductions in the Nab-Pac dose, and 47% of patients had reductions in the Gem dose; in the Gem arm, 33% of patients had dose reductions
- the use of second-line therapies was balanced between the treatment arms (38% in the Nab-Pac+Gem arm and 42% in the Gem arm); although not permitted by protocol, a small number (6%) of patients in the Gem arm received Nab-Pac+Gem as a second-line treatment.

At the time of the updated survival analysis[37] (9 May 2013 data cut-off), the median duration of treatment was 3.4 months in the Nab-Pac+Gem arm, and 2.3 months in the Gem arm.

4.3 Results from the CA046 trial

The validity of the method used by the company to generate OS and PFS HRs relies on the assumption that the survival hazards for patients in the two arms of the trial are proportional over time. The ERG considers that this assumption does not hold for the OS or PFS data (see Section 4.2.4). Consequently, the HRs reported throughout Section 4.3.1 and Section 4.3.2 must be interpreted with caution.

4.3.1 Final efficacy analysis (17 September 2012 data cut-off)

A summary of the primary and secondary outcome data from the CA046 trial is presented in Table 14. All analyses were carried out using data from the ITT population.

Table 14 CA046 trial primary and secondary efficacy endpoints (ITT population: 17 September 2012 data cut-off)

Efficacy variable	Nab-Pac+ Gem (N=431)	Gem (N=430)	HR or RRR (95% CI)*	p-value
OS				
Events, n (%)	333 (77)	359 (83)	-	-
Censored, n (%)	98 (23)	71 (17)	-	-
Median months (95% CI)	8.5 (7.9 to 9.5)	6.7 (6.0 to 7.2)	0.72 (0.62 to 0.83)	<0.001
Survival rate, % (95% CI) 6 months 12 months 18 months 24 months	 67 (62 to 71) 35 (30 to 39) 16 (12 to 20) 9 (6 to 13)	 55 (50 to 60) 22 (18 to 27) 9 (6 to 12) 4 (2 to 7)	 - - - -	 <0.001 <0.001 0.008 0.02
PFS (independent review)				
Events, n (%)	277 (64)	265 (62)	-	-
Censored, n (%)	154 (36)	165 (38)	-	-
Median months (95% CI)	5.5 (4.5 to 5.9)	3.7 (3.6 to 4.0)	0.69 (0.58 to 0.82)	<0.001

Efficacy variable	Nab-Pac+ Gem (N=431)	Gem (N=430)	HR or RRR (95% CI)*	p-value
PFS rate, % (95% CI) 6 months 12 months 18 months	 44 (39 to 50) 16 (12 to 21) 5 (2 to 11)	 25 (20 to 30) 9 (5 to 14) 7 (3 to 13)	 - - -	 - - -
PFS (investigator assessment)				
Events, n (%)	327 (76)	348 (81)	-	-
Censored, n (%)	104 (24)	82 (19)	-	-
Median months (95% CI)	5.3 (4.4 to 5.5)	3.5 (3.3 to 3.7)	0.61 (0.52 to 0.71)	<0.001
PFS rate, % (95% CI) 6 months 12 months	 41 (35.6 to 45.6) 12 (8.3 to 16.0)	 18 (13.8 to 21.9) 4 (1.9 to 6.5)	 - -	 - -
ORR (independent review)				
No. of patients with response	99	31	3.19 (2.18 to 4.66)	<0.001
% (95% CI)	23 (19 to 27)	7 (5 to 10)	-	-
No. of patients with disease control**	206	141	1.46 (1.23 to 1.72)	<0.001
% (95% CI)	48 (43 to 53)	33 (28 to 37)	-	-
Best response, n (%): Complete response Partial response Stable disease Progressive disease Not evaluable No post-baseline assessment	 1 (<1) 98 (23) 118 (27) 86 (20) 56 (13) 72 (17)	 0 31 (7) 122 (28) 110 (26) 80 (19) 87 (20)	 - - - - - -	 - - - - - -
ORR (investigator assessment)				
No. of patients with response	126	33	3.81 (2.66 to 5.46)	<0.001
% (95% CI)	29 (25 to 34)	8 (5 to 11)	-	-
Best response, n (%): Complete response Partial response Stable disease Progressive disease Not evaluable No post-baseline assessment	 6 (1) 120 (28) 96 (22) 96 (22) 43 (10) 70 (16)	 0 33 (8) 105 (24) 156 (36) 50 (12) 86 (20)	 - - - - - -	 - - - - - -

CI=confidence interval; HR=hazard ratio; ITT=intention-to-treat; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; RRR=response rate ratio.
* HRs are provided for OS and PFS; the RRRs are provided for the ORRs
** Disease control included confirmed complete response, confirmed partial response, and stable disease for at least 16 weeks
Source: CS, Table 13

Overall survival

Treatment with Nab-Pac+Gem statistically significantly improved median OS in comparison to treatment with Gem (8.5 months versus 6.7 months; HR=0.72, 95% CI: 0.62 to 0.83). The

incremental OS benefit of treatment with Nab-Pac+Gem was 1.8 months. The effect of Nab-Pac+Gem was consistent over time as survival rates were statistically significantly higher in the Nab-Pac+Gem arm than in the Gem arm at both 1 year and 2 years ($p<0.001$ and $p=0.02$, respectively).

The company also performed a multivariate analysis of OS (using a Cox PH regression model) to evaluate treatment effect adjusted for the stratification factors used at randomisation (geographic region, KPS, presence of liver metastases). The results of this analysis also suggest a statistically significant improvement in OS for patients in the Nab-Pac+Gem arm in comparison to patients in the Gem arm (HR=0.71, 95% CI: 0.61 to 0.83; $p<0.0001$). The results suggest that lower KPS (70 to 80) and presence of liver metastases are independently associated with a higher risk of death.

All the sensitivity analyses carried out by the company showed a statistically significant OS treatment effect in favour of patients treated with Nab-Pac+Gem. The analyses included a sensitivity analysis of subsequent therapy, where survival data were censored at the time that subsequent treatment began. Median OS was statistically significantly longer for patients treated with Nab-Pac+Gem than for patients treated with Gem (9.4 months vs 6.8 months; HR=0.68, 95% CI: 0.56 to 0.82; $p<0.001$).

The company also outlined details of post-hoc exploratory analyses (CS, p65). Median survival in patients who received second-line treatment was significantly longer in the Nab-Pac+Gem group than in the Gem group (12.8 months versus 9.9 months; HR=0.76, 95% CI: 0.61 to 0.95; $p=0.015$). Median OS was also statistically significantly longer for patients treated until disease progression in the Nab-Pac+Gem group than for patients in the Gem group (9.8 months versus 7.5 months, $p<0.001$).

The company states that the results of these post-hoc analyses suggest that prolonged first-line treatment exposure and ability to receive subsequent therapies can further improve survival. The ERG notes that, irrespective of first-line treatment, compared with the overall trial population, median OS is longer within both the subgroup of patients receiving second-line treatment and the subgroup of patients who were treated until disease progression. However, the ERG also notes that no formal statistical testing was performed to detect differences between these subgroups and the overall trial population and it is, therefore, not possible to conclude that prolonged treatment, or the use of subsequent therapy, improves survival in this patient population.

Subgroup analyses for overall survival

The results of the subgroup analyses are reported in the CS (Figure 8, p74). The estimate of treatment effect favoured treatment with Nab-Pac+Gem rather than Gem in all subgroups, except patients with normal CA19-9 levels for whom no conclusions could be drawn. The company highlights that patients with more advanced disease generally benefited from treatment with Nab-Pac+Gem more than patients with less advanced disease, i.e., patients with poorer KPS (70-80), patients with >3 metastatic sites, and patients with elevated CA19-9 levels. The ERG agrees with the company's observations but notes that these analyses were not powered to detect subgroup differences and, therefore, it is not possible to draw firm conclusions about treatment effect in patients with more advanced disease.

The company also highlights that although no UK patients were enrolled in the CA046 trial, the subgroup of patients from Western Europe had the same reduction in risk of death as the total patient population (HR=0.72) for Nab-Pac+Gem versus Gem alone. Furthermore, the company refers to a subgroup analysis of the dataset for the updated OS analysis (data cut-off: 9 May 2013), the results from which show that median OS in the Western Europe cohort was 3.8 months greater in the Nab-Pac+Gem group (n=38) than in the Gem group (n=38), although this difference was not statistically significant (HR=0.82, 95% CI: 0.48 to 1.4; p=0.471).[38] The ERG notes that the number of patients in this latter subgroup was relatively small, so the absence of a statistically significant result is not of concern.

Progression-free survival

Treatment with Nab-Pac+Gem statistically significantly improved median PFS in comparison to treatment with Gem. Table 14 shows an incremental PFS benefit of 1.8 months for both PFS by independent review (HR=0.69, 95% CI: 0.58 to 0.82) and PFS by investigator assessment (HR=0.61, 95% CI: 0.52 to 0.71). At 1 year, PFS rates were greater in the Nab-Pac+Gem group compared with the Gem group (16% versus 9%, independent review; 12% versus 4%, investigator assessment). The ERG is not concerned about the differences between investigator assessment and independent review as the independent reviewer often has less information to work with than the trial investigator.

The ORR assessed by independent review was statistically significantly higher for patients treated with Nab-Pac+Gem than for those treated with Gem (23% versus 7%; response rate ratio [RRR]=3.19, 95% CI: 2.18 to 4.66; p<0.001). This finding was supported by ORR assessed by investigator which was also statistically significantly higher for patients treated with Nab-Pac+Gem than for patients treated with Gem (29% versus 8%; RRR=3.81, 95% CI: 2.66 to 5.46; p<0.001).

4.3.2 Updated survival analysis (9 May 2013 data cut-off)

Results of the updated post-hoc OS analysis[37] (data cut-off: 9 May 2013) are provided in Table 15.

Table 15 Updated survival estimates in the CA046 trial (ITT population; 9 May 2013 data cut-off)

	Nab-Pac+Gem (N=431)	Gem (N=430)	HR (95% CI)	p-value
Events, n (%)	380 (88)	394 (92)	-	-
Censored, n (%)	51 (12)	36 (8)	-	-
Median months (95% CI)	8.7 (7.9 to 9.7)	6.6 (6.0 to 7.2)	0.72 (0.62 to 0.83)	<0.0001
Survival rate, % (95% CI) 6 months 12 months 24 months 36 months 42 months	 66 (62 to 71) 35 (31 to 40) 10 (6 to 13) 4 (2 to 7) 3 (1 to 6)	 55 (50 to 60) 22 (18 to 26) 5 (2, 7) 0 0	-	-

CI=confidence interval; HR=hazard ratio; ITT=intention-to-treat
Source: CS, Table 14

The reported updated OS HR of 0.72 (95% CI: 0.62 to 0.83) is in accordance with the findings of the primary analysis, supporting the evidence for a statistically significant benefit of treatment with Nab-Pac+Gem in comparison to Gem (8.7 months versus 6.6 months). The incremental OS benefit for Nab-Pac+Gem versus Gem is 2.1 months. The company states that the results of the updated OS analysis[37] show mean OS to be 11.1 months in the Nab-Pac+Gem arm and 8.7 months in the Gem arm.

Results from all sensitivity analyses demonstrated a statistically significant improvement in OS for patients treated with Nab-Pac+Gem compared with those treated with Gem. Results from a multivariate regression analysis (using a Cox PH model) adjusting for the randomisation stratification factors also demonstrated a statistically significant treatment benefit in favour of Nab-Pac+Gem versus Gem (HR=0.68, 95% CI: 0.57 to 0.80; p<0.001).

4.4 Health-related quality of life

The company reports (CS, p69) that HRQoL data were not collected during the CA046 trial but has presented information from three different sources, namely the SIEGE[28] trial, the LAPACT[30] trial and a cross-sectional study[32] that was conducted in the USA. Key details about these trials are presented in Table 16.

The SIEGE[28] trial has the greatest relevance to the current appraisal as it is a UK-based randomised trial that recruited patients with metastatic pancreatic cancer. However, the

SIEGE[28] trial was designed to compare two dose schedules of Nab-Pac+Gem and only the 'concomitant arm' (i.e. treatment with Gem immediately after treatment with Nab-Pac) is relevant to the appraisal under discussion. The LAPACT[30] trial is an ongoing phase II single arm trial that is recruiting patients with locally advanced pancreatic cancer and the Picozzi[32] study is a small US-based retrospective study that compares data from patients treated with Nab-Pac+Gem with patients who did not receive treatment for their metastatic pancreatic cancer.

The company summarises (CS, p70) the HRQoL data from the SIEGE[28] trial that were presented at the 2017 American Society of Clinical Oncology (ASCO) conference. The company describes the data as 'early' and states that the Global Health Status scores collected using the EORTC QLQ-C30 questionnaire were stable across time; however, data were only available from a small number of patients (n=22) at week 24 of the trial. The EQ-5D-5L data from the SIEGE[28] trial were used as the basis for estimating utility values that were used in cost effectiveness scenario analyses.

Table 16 Key details about studies mentioned in the company submission that collected HRQoL data

	Patient population	Geographical region	Study design Number patients	Data collected	ERG comment
SIEGE[28]	Metastatic pancreatic ductal carcinoma	UK	Phase II randomised trial comparing sequential Nab-Pac+Gem (n=71) with concomitant Nab-Pac+Gem (n=75)	EORTC QLQ-C30 EQ-5D-5L	UK-based trial Non-comparative data only Only early results available
LAPACT[30]	Locally advanced pancreatic adenocarcinoma	Not reported	Phase II single arm ongoing Nab-Pac+Gem 36 respondents	EORTC QLQ-C30	Ongoing trial Small number of respondents Locally advanced disease
Picozzi[32]	Metastatic pancreatic cancer	USA	Cross sectional study Nab-Pac+Gem (n=26) No treatment (n=29)	EORTC QLQ-C30 EORTC QLQ-PAN26 EQ-5D	Real world evidence Small retrospective study Based in USA

4.5 Adverse events reported in the CA046 trial

Details of the AEs experienced by patients participating in the CA046 trial (data cut-off 17 September 2012) are presented in Section 4.12 of the CS (p106-121). The ERG notes from the CSR (p135) that the median treatment duration for patients treated with Nab-Pac+Gem was 3.9 months, compared to 2.8 months for patients treated with Gem. It is also stated in

the CSR that the median number of treatment doses given to patients in the Nab-Pac+Gem arm was 12; nine doses were given to patients in the Gem arm.

The company discusses AEs in terms of being treatment-emergent or treatment-related. Treatment-emergent AEs (TEAEs) are defined as any AEs that begin or increase in intensity after study drug initiation up to 30 days after the last dose or the end of the study, whichever is later. Treatment-related AEs (TRAEs) are defined as AEs that were considered by the trial investigator to be either possibly, probably or definitely related to the study drug.

Summary of safety data are summarised in Table 21 of the CS (p107) and are reproduced in Table 17. The company observes that 99% of patients treated with Nab-Pac+Gem reported at least one TEAE and that 96% of these were assessed as being treatment-related. Compared with patients in the Gem arm, patients in the Nab-Pac+Gem arm experienced more Grade ≥3 TRAEs (77% vs 50%) and more AEs (any grade) leading to treatment discontinuation (35% versus 24%), dose reduction (50% versus 31%) or dose delay (66% versus 48%). The proportion of treatment-emergent deaths was the same in both trial arms (4%). The company states that the higher rates of Grade ≥3 AEs and SAEs in the Nab-Pac+Gem arm compared with the Gem arm were expected as additive toxicity is often observed when administering anti-chemotherapy agents concurrently (CS, p106-107).

Table 17 Overview of safety data in CA046 trial

Category of event	Nab-Pac+Gem N=421 n (%)	Gem N=402 n (%)
Patients with at least one TEAE	417 (99)	395 (98)
Patients with at least one treatment-related TEAE	403 (96)	371 (92)
Patients with at least one SAE	212 (50)	172 (43)
Patients with at least one treatment-related SAE	121 (29)	53 (13)
Patients with at least one TRAE leading to dose reduction	209 (50)	125 (31)
Patients with at least one AE leading to dose delay	276 (66)	192 (48)
Patients with at least one Grade ≥3 AE	374 (89)	303 (75)
Patients with at least one Grade ≥3 TRAE	325 (77)	203 (50)
Patients with at least one TEAE leading to treatment discontinuation	149 (35)	95 (24)
Patients with at least one TEAE with outcome of death	18 (4)	18 (4)

AE=adverse event; SAE=serious adverse event; TEAE=treatment-emergent adverse event; TRAE-treatment-related adverse event.
Source: CS, Table 21

Treatment-emergent adverse events

The company lists the incidence of TEAEs of all grades experienced by 40% or more of patients in either treatment arm (CS, p107-108). The company reports that the most frequently reported events in the Nab-Pac+Gem arm (in descending order) were fatigue

(59%), peripheral neuropathy (54%), nausea (54%), alopecia (50%), peripheral oedema (46%), diarrhoea (44%), anaemia (42%), neutropenia (42%) and pyrexia (41%). The ERG notes that in the Gem arm, the most frequently reported TEAEs were nausea (48%), fatigue (46%), anaemia (33%), peripheral oedema (31%) and neutropenia (30%). The TEAEs with the greatest observed differences between treatment groups were peripheral neuropathy (54% in the Nab-Pac+Gem arm and 13% in the Gem arm) and alopecia (50% in the Nab-Pac+Gem arm and 5% in the Gem arm).

Table 22 in the CS (p108-109) lists the incidence of TEAEs assessed as Grade ≥3 in more than 5% of patients; this table is replicated in Table 18 of this ERG report. The company comments that there were more AEs reported by patients treated with Nab-Pac+Gem than by patients treated with Gem (89% versus 75%). The company points out that the most frequently reported AEs in the Nab-Pac+Gem arm were neutropenia (33%), fatigue (18%), metabolism and nutritional disorders (18%), peripheral neuropathy (17%), thrombocytopenia (13%) and anaemia (12%). The ERG notes that the most frequently reported AE in the Gem arm was neutropenia (21%).

Table 18 Treatment-emergent adverse events (Grade ≥3) in the CA046 trial (≥5% in either group)

Category of event	Nab-Pac+Gem N=421 n (%)	Gem N=402 n (%)
At least one Grade ≥3 AE	374 (89)	303 (75)
Blood and lymphatic system disorders	202 (48)	128 (32)
Neutropenia	138 (33)	85 (21)
Thrombocytopenia	53 (13)	33 (8)
Anaemia	49 (12)	32 (8)
Leukopenia	39 (9)	15 (4)
General disorders and administration site conditions	132 (31)	76 (19)
Fatigue	77 (18)	37 (9)
Asthenia	29 (7)	17 (4)
Gastrointestinal disorders	114 (27)	92 (23)
Abdominal pain	27 (6)	32 (8)
Diarrhoea	26 (6)	6 (1)
Nausea	27 (6)	14 (3)
Vomiting	25 (6)	15 (4)
Nervous system disorders	82 (19)	19 (5)
Peripheral neuropathy SMQ	70 (17)	3 (1)
Metabolism and nutritional disorders	76 (18)	48 (12)
Dehydration	31 (7)	10 (2)
Decreased appetite	23 (5)	8 (2)
Respiratory, thoracic and mediastinal disorders	41 (10)	45 (11)
Pulmonary embolism	19 (5)	26 (6)
Vascular disorders	41 (10)	39 (10)
Deep vein thrombosis	21 (5)	22 (5)

AE=adverse event; SMQ=standardised MeDRA (Medical Dictionary for Regulatory Activities) query
Source: CS, Table 22

Serious adverse events

Appendix 3 of the CS reports the overall incidence of SAEs to be 50% in the Nab-Pac+Gem arm and 43% in the Gem arm. The majority of SAEs were reported to have similar rates across both arms of the trial. The exception was pyrexia (6% Nab-Pac+Gem versus 2% Gem). Febrile neutropenia was experienced by 3% of patients in the Nab-Pac+Gem arm compared to <1% of patients in the Gem arm.

The company (CS, p112) reports the AE rates according to particular subgroups of patients that were not pre-planned. These include age (≤65 years, ≥65 years, and ≥75 years), males versus females and geographical region.

It is recorded in the CS (p112-113) that the rates of AEs and SAEs were higher in older patients (≥65 years) treated with Nab-Pac+Gem than in the overall treated population. The CS also reports that for patients aged ≥75 years, more frequent Grade 3 TEAEs, SAEs, TEAEs with an outcome of death and TEAEs leading to study discontinuation were recorded in the Nab-Pac+Gem arm than in the Gem arm. The number of patients aged ≥75 years of age included in the study was small (n=84), and therefore, comparisons of TEAEs in this subgroup should be interpreted with caution. The ERG notes that the EMA's marketing authorisation[9] for Nab-Pac+Gem contains a warning regarding the increased risk of AEs in the ≥75 years of age group and states that use of Nab-Pac for the treatment of patients ≥75 years should be carefully considered.

The company reports that TEAEs with a ≥10% difference in women compared with men were neutropenia (49% versus 36%), anaemia (49% versus 36%), vomiting (44% versus 29%), and urinary tract infection (17% versus 4%). Neutropenia was the only Grade 3 or higher TEAE reported with a >5% difference in women than men (40% versus 27%).

The overall incidence of TEAEs, Grade 3 or higher TEAEs, and SAEs was similar between patients from the four different geographic regions (North America, Western Europe, Eastern Europe and Australia) that were considered.

Peripheral neuropathy

The company states (CS, p109) that the majority of cases of Grade ≤3 neuropathy could be reversed and managed by delaying further treatment or reducing the dose until the condition improved to Grade ≤1. The company also reports that a (not pre-specified) subgroup analysis showed that patients who developed Grade 3 peripheral neuropathy had increased treatment exposure and thus experienced significantly better OS, PFS, ORR compared to those who did not develop peripheral neuropathy (CS, p109, Table 23, replicated in Table 19). The company reports that peripheral neuropathy was rapidly reversible with treatment interruption and that the median time to improvement to Grade 1 severity was 29 days. The ERG considers that 29 days is a substantial period for a patient with metastatic pancreatic cancer. The ERG notes from the CSR that peripheral neuropathy was the most common reason for treatment discontinuation (8%) in the Nab-Pac+Gem arm.

Table 19 Treatment exposure and efficacy outcomes by grade of peripheral neuropathy in the Nab-Pac+Gem group of the CA046 trial

	Grade of peripheral neuropathy				HR or RRR (95% CI)* p-value
	0	1	2	3	
OS, median months (95% CI)	5.9 (4.7 to 6.9)	9.0 (8.3 to 12.3)	12.6 (9.6 to 15.7)	14.9 (11.9 to 19.2)	0.33 (0.23 to 0.48) p<0.0001
PFS, median months (95% CI)	3.5 (3.1 to 3.8)	5.6 (4.5 to 6.2)	9.3 (7.2 to 12.6)	9.1 (7.5 to 11.5)	0.27 (0.18 to 0.41) p<0.0001
ORR, % (95% CI)	8 (4.4 to 1.24)	29 (20.3 to 39.3)	43 (30.0 to 55.9)	43 (31.1 to 55.3)	5.54 (3.18 to 9.67) p<0.0001
Median treatment cycles (range)	1 (1–13)	4 (1–17)	6 (1–2)	6 (1–22)	-

CI=confidence interval; HR=hazard ratio; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; RRR=response rate ratio
* Patients with Grade 3 peripheral neuropathy versus no peripheral neuropathy
Source: CS, Table 23

Toxicities

Further post-hoc subgroup analyses were conducted to evaluate the effect that dose modifications due to toxicities have on treatment exposure and efficacy (Table 20). The company states that toxicity management is an important part of the use of Nab-Pac+Gem and that results of dose modification due to toxicities are similar to the results of the post-hoc subgroup analysis of patients with peripheral neuropathy: dose modifications result in greater treatment exposure and thus greater clinical efficacy. The company suggests that appropriate dose modifications should be encouraged to accommodate the safe use of Nab-Pac+Gem in clinical practice and that dose reductions do not negatively influence patient outcomes.

Clinical advice to the ERG is that patients who benefit most from Nab-Pac+Gem are more likely to stay on treatment for longer with the resultant cumulative toxicity requiring dose reduction or delay. Patients with resistance or early disease progression are likely to discontinue treatment before dose modification is needed and would inevitably have poorer survival.

Table 20 Treatment exposure and efficacy outcomes by dose modifications in the Nab-Pac+Gem arm of the CA046 trial

	Dose reductions			Dose delays		
	No dose reduction (n=249)	**≥1 dose reduction (n=172)**	**HR or RRR (95% CI) p-value**	**No dose delay (n=121)**	**≥1 dose delay (n=300)**	**HR or RRR (95% CI) p-value**
OS, median months	6.9	11.4	1.93 (1.53 to 2.44) p<0.0001	6.2	10.1	2.05 (1.59 to 2.63) p<0.0001
PFS, median months	3.8	8.8	2.62 (2.01 to 3.42) p<0.0001	3.4	6.6	2.80 (2.13 to 3.69) p<0.0001
ORR, %	16	34	0.49 (0.34 to 0.69) p<0.0001	10	29	0.34 (0.19 to 0.60) p<0.0001

CI=confidence interval; HR=hazard ratio; OS=overall survival; ORR=overall response rate; PFS=progression-free survival; RRR=response rate ratio
Note: The HR for death is provided for OS, and the HR for progression or death is provided for PFS, with a HR of >1 favouring dose modification; the RRRs are provided for ORRs, with a RRR of <1 favouring dose modification
Source: CS, Table 24

Additional safety data

Additional safety data presented in the CS (p114-117) are summarised in Appendix 1 of this ERG report. Briefly, the additional AE data are derived from the SIEGE trial,[28] two small cohorts[39,40] of patients who were treated with Nab-Pac+Gem between October 2013 and October 2015 in the Lancashire and South Cumbria Cancer Network (n=32) and in South West Wales (n=17). Further data describing patients (n=208) who were treated in centres in Italy[23] are also presented.

The only data available from the SIEGE trial[28] are taken from a poster presented at the ASCO conference in January 2017. In comparison to the CA046 trial, the overall proportion of patients in the SIEGE trial[28] who experienced Grade ≥3 AEs was similar (89% versus 82% respectively). The rates of specific Grade ≥3 AEs reported by patients in the SIEGE trial[28] were also similar to, or lower than, rates reported in the CA046 trial. However, 5.4% of patients in the SIEGE trial[28] experienced sepsis, whilst no cases of sepsis were reported in the CA046 trial.

The only data available from the retrospective study of elderly patients (n=208) treated in Italian centres are from a poster presentation given at the 2015 ESMO conference. The safety data appear to be similar to those reported during the CA046 trial.

The ERG considers that the data available from the cohorts of patients based in Lancashire and South Cumbria and in Wales are difficult to interpret due to the small numbers of participants.

4.6 ERG summary and critique of the indirect evidence

4.6.1 Trials identified for inclusion in network meta-analysis

In addition to the CA046 trial, 16 trials met the secondary eligibility criteria for the company's systematic review. In the previous appraisal of Nab-Pac+Gem (TA360[14]), the ERG and the NICE Appraisal Committee considered that the most appropriate network of evidence to use in the company's NMA was the network that only included trials that reported data for the metastatic pancreatic cancer population. Therefore, in their NMA, the company only used data from such trials. The ERG notes that the company included trials that recruited metastatic pancreatic cancer patients, regardless of histology, whereas the population of interest to this appraisal is the metastatic pancreatic adenocarcinoma population. The ERG considers that the company's approach is appropriate as approximately 80–95% of all pancreatic cancers are of adenocarcinoma histology and, therefore, the populations of trials that recruited all metastatic pancreatic cancer patients consist largely of patients with metastatic adenocarcinoma of the pancreas.

Following production of the network of evidence, studies that had been excluded from the TA360[14] systematic review based on intervention were re-assessed for inclusion in the current NMA. One trial (Rocha Lima 2004[41]) which had previously been excluded was included in the current NMA as the trial provided data for the comparison of treatment with Gem versus Gem+Irinotecan in the metastatic pancreatic adenocarcinoma population. This comparison was included in the network of evidence due to its inclusion in the four-arm trial reported by Kulke (2009).[42] No other trials (in addition to the Rocha Lima 2004 trial[41]) were included in the NMA on this basis.

The 10 trials[6,7,12,41-47] included in the company's NMA are listed in Table 21. The company states that these trials either exclusively enrolled patients with metastatic pancreatic cancer or metastatic pancreatic adenocarcinoma, or reported a subgroup analysis for these patient populations.

Table 21 RCTs included in the company's NMA

Trial name	Design	Population	Treatment arms	Primary outcome	Key secondary outcomes
ACCORD[7]	Phase II/III, parallel-group RCT	Adult patients with previously untreated mPAC and a WHO PS score of 0–1	FOLFIRINOX (n=171) Gem (n=171)	OS	PFS, ORR, HRQoL, safety
Boeck 2008[43]	Phase II, parallel-group, open-label RCT	Adult patients with previously untreated mPC or LAPC and a KPS score ≥60	Gem+Cap (n=64) Gem+Oxaliplatin (n=63) Cap+Oxaliplatin (n=61)	PFS	OS, ORR, safety
CA046[12]	Phase III, parallel-group, open-label RCT	Adult patients with previously untreated mPAC and a KPS score ≥70	Nab-Pac+Gem (n=431) Gem (n=430)	OS	PFS, ORR, safety
CALGB 89904[42]	Phase II, parallel-group, open-label RCT	Adult patients with previously untreated mPAC and an ECOG PS of 0–2	Gem+Cisplatin (n=66) Gem+Docetaxel (n=65) Gem+Irinotecan (n=64) Gem FDR (n=64)	OS	TTP, ORR, safety
Chao 2013[44]	Parallel-group, open-label, RCT	Adult patients with previously untreated mPC in Taiwan	Gem+Cisplatin (n=21) Gem (n=25)	ORR	OS, TTP, HRQoL, safety
FRE-GERCOR-GEMOX-D99-2[45]	Phase III RCT	Adult patients with previously untreated mPAC or LAPC and a WHO PS score of 0–2	Gem+Oxaliplatin (n=163) Gem (n=163)	OS	PFS, ORR, safety
Heinemann 2006[46]	Phase III, parallel-group, open-label RCT	Adult patients with previously untreated mPC or LAPC and a KPS score of 70 or more	Gem+Cisplatin (n=98) Gem (n=97)	OS	PFS, ORR
Rocha Lima 2004[41]	Phase III, parallel-group, open-label RCT	Adult patients with previously untreated mPAC or LAPC and an ECOG PS of 0–2	Gem+Irinotecan (n=180) Gem (n=180)	OS	Tumour response, TTP, safety
Scheithauer 2003[6]	Phase II, parallel-group RCT	Adult patients with previously untreated mPAC and a KPS score of 50 or more	Gem+Cap (n=41) Gem (n=42)*	PFS	OS, ORR
Wang 2015[47]	Phase II, parallel-group, open-label RCT	Adult patients with previously untreated mPC and an ECOG PS of 0–2 in Taiwan	Gem+Erlotinib (n=44) Gem (n=44)	DCR	ORR, OS, PFS

DCR=disease control rate; ECOG=Eastern Cooperative Oncology Group; FDR=fixed dose rate; HRQoL=health-related quality of life; KPS=Karnofsky performance status; LAPC=locally advanced pancreatic cancer; mPAC=metastatic pancreatic adenocarcinoma; mPC=metastatic pancreatic cancer; NMA=network meta-analysis; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; PS=performance status; RCT=randomised controlled trial; TTP=time-to-progression; WHO=World Health Organization
*Gem monotherapy administered at the higher dose of 2,200mg
Source: CS, adapted from Table 15, Rocha Lima (2004)[41]

The ERG notes that seven[41-47] of the 10 trials included in the company's NMA provide evidence for comparators that are not relevant to the decision problem. The set of comparators that are relevant to the decision problem, i.e. Nab-Pac+Gem, Gem, FOLFIRINOX and Gem+Cap, is referred to in the remainder of this report as the 'decision comparator set'.

4.6.2 ERG rationale for focusing on a reduced network of evidence

The company provides details of the patient characteristics and trial methodology for each of the 10 trials[6,7,12,41-47] included in the base case NMA (CS, Appendix 4). A summary of the key differences between the studies included in the base case NMA is provided in Appendix 10.4.

Generally, the ERG considers that the trial methodology and patient characteristics of the 10 included trials are similar enough that conducting a NMA that includes these trials is appropriate. However, as mentioned in Section 4.6.1, seven[41-47] of the trials included in the base case NMA provide evidence for comparators that are not relevant to the decision problem. The ERG notes that a connected network can be formed by including only trials that compare interventions included in the decision comparator set. According to guidance in NICE Technical Support document 1,[48] there is no specific need to include comparators other than those in the decision comparator set, unless such an extension is required to produce a connected network.

The company's rationale for including additional trials in the network is that evidence from these trials provides feedback loops, meaning that the consistency of direct and indirect evidence can be considered. While the ERG is aware that it is stated within NICE Technical Support Document 1[48] that one advantage of including additional comparators is the ability to investigate consistency in the network, it is also stated that such extension of the network should not be used in the base case analysis. The disadvantage of extending the network is the possibility that effect modifiers will be introduced as trials of more remotely connected treatments are likely to have different patient populations compared to the patient population of interest. This seems to be the case for the company's NMA as extending the network leads to the inclusion of some trials with exclusively Asian populations. Furthermore, extending the network results in the inclusion of trials[44,47] with primary outcomes other than OS and PFS (i.e. trials that were not powered to detect differences in OS or PFS), and trials that do not report HR data[6,41-44,47] (meaning that the company had to estimate HRs, or use median survival data, see Section 4.6.4). Consequently, the ERG considers that results from a NMA that includes only trials that compare treatments in the decision comparator set are

more informative than results from a NMA that includes data from all 10 of the trials[6,7,12,41-47] listed in Table 21.

The company performed a sensitivity analysis (sensitivity analysis 2 [SA2], see Section 4.6.4) that included only trials that compared treatments specified in the decision comparator set and the ERG considers that this sensitivity analysis should have formed the company's base case NMA. Restricting the network to only trials that compare treatments in the decision comparator set results in a network of trials that has patient populations that are relevant to the decision problem; all trials have at least some sites in European countries, and all comparators are relevant to UK clinical practice. In addition, for the base case NMA, the company incorporated median survival data due to the absence of both reported HRs and K-M data for some included studies. All studies in the reduced network report HR data (or provide K-M data from which HRs can be estimated) for both OS and PFS; therefore, analyses using this reduced network are not subject to the limitations of using median OS data for some comparisons. Further details of the analyses conducted by the company are provided in Section 4.6.4.

4.6.3 Characteristics of trials included in the reduced network of evidence

As the ERG considers the results of the company's analyses that use the reduced network of evidence to be the most valid, the ERG has presented a comparison of the trial methodology and baseline patient characteristics of studies included in this reduced network in the Appendices to this ERG report (Appendix 10.5 and Appendix 10.6). The ERG notes that the dosing regimen of Gem used in the Scheithauer trial[6] differs to the dosing regimen used in the other studies in the network. However, clinical advice to the ERG is that this difference would have little impact on the NMA results. Generally, the ERG considers that the trials in the reduced network are sufficiently similar for the data collected in these trials to be synthesised in a NMA.

4.6.4 Methodological approach to the network meta-analysis

The company's NMA was conducted to provide estimates of relative treatment efficacy (in terms of OS and PFS) between the comparators included in each network of evidence. The company states that it was not possible to use the NMA to compare the safety of the drugs of interest due to a paucity of comparable safety data.

The company performed the base case NMA and three sensitivity analyses; sensitivity analysis 1 (SA1), sensitivity analysis 2 (SA2) and sensitivity analysis 3 (SA3). Each of these analyses is described in Table 22.

Table 22 Base case NMA and sensitivity analyses

Analysis	Description
Base case analysis	Exclusively metastatic pancreatic cancer population data Extensive set of comparators (to provide feedback loops between comparators of interest) Combination of HR and median survival data (HR data where reported/estimated, otherwise median survival) Fixed-effects model
Sensitivity analysis 1 (SA1)	Identical to the base case analysis, but with a random-effects model instead of a fixed-effects model
Sensitivity analysis 2 (SA2)	Reduced set of comparators that are relevant to the NICE scope The network is a reduced version of the network used for the base case analysis and is limited to data from the metastatic pancreatic cancer population All trials included in the reduced network report HR data Fixed-effect model
Sensitivity analysis 3 (SA3)	Identical to the base case analysis, except that metastatic pancreatic cancer median survival data is replaced with locally advanced pancreatic cancer HR data where metastatic pancreatic cancer HR data [absolute or K-M data] were not reported

HR=hazard ratio; K-M=Kaplan-Meier; NMA=network meta-analysis
Source: CS, p82-83

The network of evidence used for the base case analysis, SA1 and SA3, is presented in Figure 3. The network of evidence used for SA2 and the ERG requested analysis is provided in Figure 4.

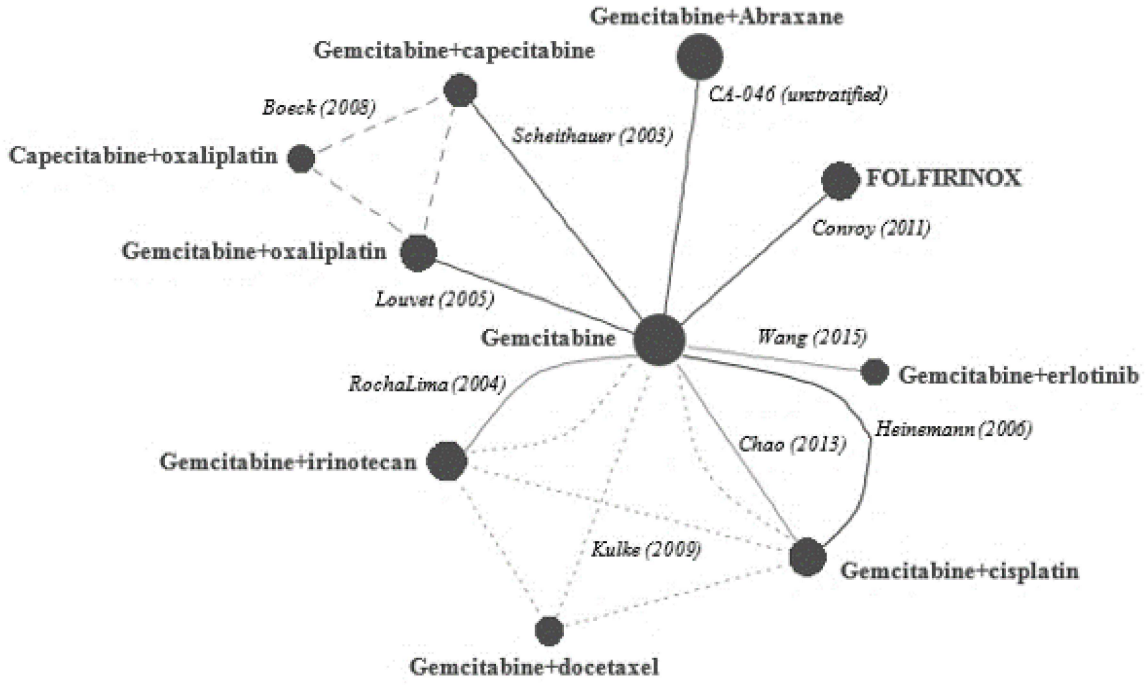

Figure 3 Network of evidence: base case analysis, SA1 and SA3

Solid lines represent two-arm studies; dashed lines represent three-arm studies; dotted lines represent four-arm studies; node sizes are proportional to the number of patients treated with the respective intervention.
Source: CS, adapted from Figure 9 (colours removed)

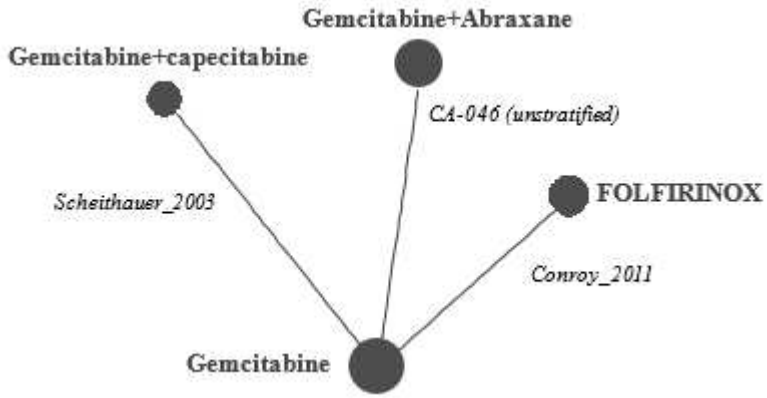

Figure 4 Network of evidence: SA2 and the ERG requested analysis

Node sizes are proportional to the number of patients treated with the respective intervention
HR=hazard ratio
Source: CS, adapted from Figure 14 (colours removed)

As previously mentioned, the ERG considers that using the reduced network (i.e. including only trials that make comparisons between treatments in the decision comparator set) provides more valid results than those derived from the analyses using the wider network (i.e. base case analysis, SA1 and SA3). As the company's analysis in the reduced network (SA2) used a fixed-effects model, the ERG asked the company to provide results for this reduced network using a random-effects model, so that the impact of this model choice on the analysis using the reduced network could be evaluated. The company provided this additional analysis, which from this point onwards, will be referred to as the "ERG requested analysis".

As previously discussed in Section 4.6.3, there was a lack of clarity as to whether disease progression was investigator- or independently-assessed in most of the trials included in the NMA, and so the company analysed the PFS endpoint using both independent-assessed and investigator-assessed PFS data from the CA046 trial. As the independent assessment of PFS was the named secondary endpoint in the CA046 trial, but investigator assessment of PFS was utilised in the company's cost effectiveness model to better reflect clinical practice, the ERG considers the company's approach to be suitable.

Proportional hazards assumption

The validity of the results of all of the indirect analyses conducted by the company (i.e. base case NMA, three sensitivity analyses, and the ERG requested analysis) relies on the assumption that OS and PFS hazards are proportional in each of the trials included in the network for each analysis. The network used in the company's base case NMA, the reduced network used in SA2, and the ERG requested analysis all include the CA046 trial as this trial links Nab-Pac+Gem to Gem. As previously shown in Section 4.2.4, the PH assumption is not valid for OS or PFS data from the CA046 trial. The violation of the PH assumption for OS

and PFS in this trial compromises the networks of evidence. HRs are not an appropriate summary of treatment effect within this network, and it is not possible to know whether the reported HRs would overestimate or underestimate treatment effects estimated by the NMA. The ERG, therefore, considers that all NMA results should be interpreted with caution.

4.6.5 Assessment of risk of bias of the trials included in the network meta-analysis

The company quality assessed all of the trials included in the base case NMA using the criteria recommended by NICE (CS Appendices, Appendix 4). The ERG's summary of the company's risk of bias assessment can be found in Appendix 10.7.

The assessment of risk of bias for studies included in the reduced network is also provided in Appendix 10.8 of the ERG report. In all of the studies, randomisation was carried out appropriately, patient characteristics were balanced between treatment groups and there was no evidence to suggest that selective reporting of outcomes had occurred. The ACCORD[7] trial (FOLFIRINOX versus Gem) was judged to be at high risk of bias for unexpected imbalances in drop-outs between treatment groups as more patients in the Gem arm discontinued treatment than in the FOLFIRINOX arm, with almost twice as many patients discontinuing treatment due to disease progression. In addition, the trial by Scheithauer 2003[6] was deemed not to represent UK practice; all patients were enrolled from study centres in Austria and the dosage of Gem monotherapy (2,200mg/m^2) was not reflective of UK practice. The ERG considers that it is important to take these issues into consideration when interpreting results from the reduced network NMAs in the reduced network (SA2 and the ERG requested analysis).

4.6.6 Results from the network meta-analysis

As the ERG considers results from the reduced network NMA including only trials that make comparisons between treatments in the decision comparator set to be the most valid, only results from SA2 and the ERG requested analysis are presented in this section. Results from analyses performed using the wider network of evidence (i.e. base case analysis, SA1, and SA3) are summarised in Appendix 10.9 of the ERG report.

SA2

SA2 uses a reduced network of evidence including only trials that compare treatments in the decision comparator set. Three trials[6,7,12] evaluating four treatments are included in this analysis (as shown previously in Figure 4). For OS, all included studies reported HR data; for PFS, two studies reported HR data,[7,12] while one trial[6] presented a K-M curve from which a HR could be estimated.

Relative effects for each of the treatments in the decision comparator set versus Nab-Pac+Gem are presented in Table 23, for the outcomes of OS and PFS by independent assessment. The company also presents the results for each treatment included in the network versus Gem for each of these outcomes in Appendix 4 of the CS.

Table 23 Results of SA2

Treatment comparison	HR (95% CrI)
OS	
Gem vs Nab-Pac+Gem	1.35 (1.17 to 1.56)
Gem+Cap vs Nab-Pac+Gem	1.10 (0.67 to 1.84)
FOLFIRINOX vs Nab-Pac+Gem	0.77 (0.58 to 1.01)
PFS by independent assessment	
Gem vs Nab-Pac+Gem	1.45 (1.22 to 1.72)
Gem+Cap vs Nab-Pac+Gem	1.17 (0.75 to 1.86)
FOLFIRINOX vs Nab-Pac+Gem	0.68 (0.51 to 0.91)

CrI=credible interval; HR=hazard ratio; OS=overall survival; PFS=progression-free survival; vs=versus
Source: CS, Figure 15 and Figure 17

For OS, Gem was shown to be statistically significantly inferior to Nab-Pac+Gem (HR=1.35, 95% CrI: 1.17 to 1.56). For Gem+Cap versus Nab-Pac+Gem, there is no evidence to suggest a difference between these two treatments in terms of OS. For FOLFIRINOX versus Nab-Pac+Gem, the HR favoured FOLFIRINOX, although this result was not statistically significant (HR=0.77, 95% CrI: 0.58 to 1.01). Compared to the base case analysis, only the HR for Gem+Cap versus Nab-Pac+Gem has been affected by using the reduced network. The direction of effect is reversed in comparison to the base case analysis, and now favours Nab-Pac+Gem, although no statistically significant differences were identified between these two treatments in either analysis. This change is due to the fact that there is more indirect evidence in the network used for the base case analysis for the comparison of Gem+Cap versus Nab-Pac+Gem than is used in the reduced network used for SA2. The evidence that contributes to the Nab-Pac+Gem versus Gem, and FOLFIRINOX versus Nab-Pac+Gem remains constant between the two networks. As previously discussed, the ERG considers that results from SA2 are more valid than those from the base case NMA.

The probabilities of being the best treatment and median ranks for OS are provided in Table 18 of the CS. The probabilities of being the best treatment are: FOLFIRINOX (0.878), Gem+Cap (0.097), Nab-Pac+Gem (0.025), and Gem (0.000). Nab-Pac+Gem is expected to be the second best treatment (probability=0.63) after FOLFIRINOX.

For PFS, Gem was shown to be statistically significantly inferior to Nab-Pac+Gem (HR=1.45, 95% CrI: 1.22 to 1.72). For Gem+Cap versus Nab-Pac+Gem, no statistically significant

differences were observed between the treatments. FOLFIRINOX was shown to be statistically significantly superior to Nab-Pac+Gem (HR=0.68, 95% CrI: 0.51 to 0.91).

The probabilities of being the best treatment and median ranks for the outcome of PFS by independent assessment are provided in Table 19 of the CS. The probabilities of being the best treatment are: FOLFIRINOX (0.982), Gem+Cap (0.013), Nab-Pac+Gem (0.005), and Gem (0.000). Nab-Pac+Gem is expected to be the second best treatment (probability=0.75) after FOLFIRINOX.

ERG requested analysis

As the company's analysis in the reduced network (SA2) uses a fixed-effects model, the ERG asked the company to provide results for this reduced network using a random-effects model so that the impact of this model choice on the analysis using the reduced network could be evaluated. The results of the ERG requested analysis are provided in Table 24.

Table 24 Results of the ERG requested analysis

Treatment comparison	HR (95% CrI)
OS	
Gem vs Nab-Pac+Gem	1.33 (0.12 to 15.43)
Gem+Cap vs Nab-Pac+Gem	1.10 (0.03 to 35.88)
FOLFIRINOX vs Nab-Pac+Gem	0.76 (0.02 to 23.48)
PFS (independent review)	
Gemcitabine vs Nab-Pac+Gem	1.43 (0.13 to 16.90)
Gem+Cap vs Nab-Pac+Gem	1.17 (0.04 to 35.16)
FOLFIRINOX vs Nab-Pac+Gem	0.67 (0.02 to 18.90)
PFS (investigator review)	
Gemcitabine vs Nab-Pac+Gem	1.65 (0.14 to 20.11)
Gem+Cap vs Nab-Pac+Gem	1.33 (0.04 to 47.00)
FOLFIRINOX vs Nab-Pac+Gem	0.77 (0.02 to 29.96)

CrI=credible interval; HR=hazard ratio; OS=overall survival; PFS=progression-free survival; vs=versus
Source=Question A5 of the company's response to the ERG clarification letter

The point estimates of the HRs are similar to those obtained in SA2, but the corresponding credible intervals are very wide. This company states that, when running this analysis, there were issues with model convergence when estimating HRs. In other words, there were not enough data in the random-effects model to obtain a precise CrI around estimates of HRs, resulting in large uncertainty in the estimates.

The company provided the ERG-requested analysis so that the impact of the choice of a fixed-effects or random-effects model on the analysis using the reduced network could be evaluated. The ERG agrees with the company that the ERG requested analysis has been

severely impacted by model convergence issues. Therefore, the ERG considers that the results of SA2 are more informative than those from the ERG requested analysis, i.e. from the fixed-effects model rather than the random-effects model because there are insufficient data to run the random-effects model. The ERG notes that slight differences in dosing regimens were identified between trials included in the reduced network but does not consider that these differences would invalidate the results of an analysis using a fixed-effects model.

4.6.7 ERG interpretation of NMA results

In summary, the ERG's considers that the OS and PFS data from the CA046 trial lack PH, and so the results of the company's NMAs should be interpreted with caution. In addition, the ERG has concerns about the relevance of the NMA results to the decision problem as there are few patients aged over 75 years of age in the trials which make up the network.

4.7 Conclusions of the clinical effectiveness section

The ERG considers that the submitted evidence largely reflects the decision problem defined in the final scope issued by NICE; however, the ERG notes the following points:

- Nab-Pac+Gem was not recommended for use in NHS England following the publication of TA360 but it has been recommended for use in NHS Wales and NHS Scotland
- the company has provided clinical effectiveness data pertaining to all comparators listed in the final scope issued by NICE; however, direct evidence is only available for the comparison of treatment with Nab-Pac+Gem versus Gem
- the company considers that Gem is the only relevant comparator to Nab-Pac+Gem
- the company considers that (i) FOLFIRINOX and Gem+Cap are not standards of care in the NHS and (ii) the introduction of Nab-Pac+Gem for use in the NHS will not displace the use of either of these comparators
- the company considers that patients who are suited to treatment with Nab-Pac+Gem are easily identified and are 'clinically distinct' from patients who are suited to treatment with FOLFIRINOX. The ERG considers that the company has yet to provide a definition of patients who are suited to treatment with Nab-Pac+Gem.

4.7.1 Clinical effectiveness evidence

Direct evidence

The direct evidence was derived from the CA046 trial. The ERG highlights the following points:

- patients in the CA046 trial were younger and fitter than patients treated in the NHS
- only 10% of patients recruited to the CA046 trial were aged ≥75 years. In the NHS, 47% of patients with pancreatic cancer are aged ≥75 years. This means that the evidence from the trial may not be relevant to a substantial number of NHS patients

- in the SmPC[9] for Nab-Pac, the EMA advises caution when considering using Nab-Pac+Gem to treat patients aged ≥75 years due to a lack of evidence of clinical efficacy and the AE profile
- results of the final efficacy analysis of the CA046 trial suggest that treatment with Nab-Pac+Gem statistically significantly improves median OS in comparison to treatment with Gem (8.5 months versus 6.7 months; HR=0.72, 95% CI: 0.62 to 0.83)
- results from the updated OS analysis are in accordance with the findings of the primary analysis, supporting the evidence for a statistically significant benefit from treatment with Nab-Pac+Gem compared to Gem (8.7 months versus 6.6 months; HR=0.72, 95% CI: 0.62 to 0.83)
- the ERG's assessment of the PH assumption for the CA046 trial data suggests that the PH assumption does not hold for either OS or PFS data and, consequently, the HRs from the CA046 trial for these outcomes should be interpreted with caution
- the most common Grade 3 and 4 AEs associated with treatment with Nab-Pac+Gem were neutropenia, fatigue, metabolism and nutritional disorders, peripheral neuropathy, thrombocytopenia and anaemia. Although these AEs are associated with treatment with either Gem or Nab-Pac monotherapies, they occur more frequently when patients are treated with the Nab-Pac+Gem combination
- no HRQoL data are available as part of the CA046 trial. The company has presented HRQoL evidence from one arm of the SIEGE trial,[28] an ongoing phase II single arm trial of patients with locally advanced pancreatic cancer who were treated with Nab-Pac+Gem and from a cross-sectional study[32] of patients with metastatic pancreatic cancer treated with Nab-Pac+Gem in the US.

Indirect evidence

The ERG highlights the following points:

- in the absence of head-to-head data for the comparisons of Nab-Pac+Gem versus FOLFIRINOX and Nab-Pac+Gem versus Gem+Cap, the company performed a NMA to obtain estimates of the relative efficacy of these comparators
- seven of the 10 trials included in the base case NMA provide evidence for comparators that are not relevant to the decision problem; the ERG considers that results from a NMA that includes only trials that compare treatments listed in the decision problem are more informative than results from a NMA that includes data from all 10 trials
- all NMA results are affected by a violation of the PH assumption within the CA046, and should be interpreted with caution.

5 COST EFFECTIVENESS

5.1 Introduction

This section provides a structured critique of the economic evidence submitted by the company in support of the use of Nab-Pac+Gem to treat patients with previously untreated metastatic adenocarcinoma of the pancreas. The two key components of the economic evidence presented in the CS are (i) a systematic review of the relevant literature and (ii) a report of the company's de novo economic evaluation. The company has also provided copies of its economic model, which were developed in Microsoft Excel.

The company submitted two copies of its economic model: the first at the beginning of the evidence review process and the second during the clarification period. The company submitted the updated model in response to an inconsistency it found between the model and the CS whilst responding to the ERG's clarification questions. The changes to the model constitute small amendments to the duration of AEs, to take into account the number of repeat events experienced by patients.

5.2 ERG comment on the company's review of the cost effectiveness evidence

5.2.1 Objective of the company's systematic review

The company performed a systematic literature review to identify and summarise the relevant cost effectiveness evidence for Nab-Pac+Gem as a treatment for previously untreated locally advanced or metastatic pancreatic cancer with the majority (>50%) of the population in any given study having metastatic disease.

Company searches

The company added to the review of cost effectiveness evidence included in the previous appraisal for this indication (TA360)[14] with updated searches from March 2014 to August 2016. The company searched MEDLINE and Embase (using Embase.com), MEDLINE In-Process (using PubMed.com), EconLit, The Cumulative Index to Nursing and Allied Health Literature (CINAHL) and The Cochrane Library (including the National Health Service Economic Evaluations Database and the Centre for Reviews and Dissemination – Health Technology Assessment Database). These searches were supplemented with searches of conference proceedings from 2013 to 2016. The search strategies used by the company are provided in Appendix 11 of the CS.

5.2.1 Eligibility criteria used in study selection

The inclusion/exclusion criteria used by the company for study selection are provided in Table 32 of the CS and are reproduced in Table 25.

Table 25 Eligibility criteria for the cost effectiveness systematic review

Criteria	Inclusion	Exclusion
Population	• Adult patients • aPAC patients, at least a proportion (50%) of whom have metastatic (or pancreatic ductal adenocarcinoma) disease • Potentially eligible for first-line therapy for metastatic disease	• Healthy volunteers • Children (age <18 years) • Diseases other than those specified in inclusion criteria
Intervention/ comparator	• Nab-Paclitaxel+gemcitabine • AND a relevant comparator from: Placebo, 5-FU, capecitabine (XELODA®), erlotinib (TARCEVA®), gemcitabine (GEMZAR®) and oxaliplatin (ELOXATIN®), monotherapy or in combination with any other therapy**	• Non-active comparisons • Comparisons outside of named list of interventions/comparators of interest
Outcomes	• ICER • Costs (unit and total) • QALYs • LYs • Incremental costs • Incremental QALYs/LYs • Model inputs (e.g. transition probabilities) • Sensitivity analyses results	•
Study type	• Full economic evaluations, such as: • Cost consequence analysis • Cost effectiveness analysis • Cost utility analysis • Cost benefit analysis • Cost minimisation analysis	• Non-systematic reviews,* letters and comment articles • Burden of illness studies and non-modelling will be excluded
Language	• Studies published in English will be included • Studies not published in English will be included and flagged***	• Studies will not be excluded based on publication language

5-FU=5-fluorouracil; aPAC=advanced pancreatic cancer; ICER=incremental cost-effectiveness ratio; LYs=life years; QALYs= quality adjusted life years
*Systematic reviews will be included and flagged for bibliography searches; **The range of potential comparators is deliberately broad. When discussing the cost effectiveness studies identified, we draw a distinction between studies that include comparators in the scope for TA360 (gemcitabine monotherapy; Gem/Cap and FOLFIRINOX) and those studies that only include the wider treatments not considered by NICE to be relevant to UK practice; *** Studies published in languages other than English will be explored only if sufficient evidence is not identified from studies published in English
Source: CS, Table 32

5.2.2 Included and excluded studies

The company's literature searches identified 404 papers. After removing duplicates, 388 papers were screened using titles and abstracts only, of which 28 papers were assessed for eligibility using the full-text version of the publication. The most common reasons for exclusion at the title and abstract stage were publication type (e.g., reviews or editorials

were excluded) or study design. After applying inclusion criteria, data from 11 papers were considered by the company to be relevant and were included in the data extraction table presented in the CS (Table 33).

5.2.3 Findings from cost effectiveness review

The company extracted data from 11 papers (Table 26). Further details of study characteristics and findings are reported in the CS, Table 33.

Table 26 Summary of company's findings from cost effectiveness review

Study	Country	Treatments	ICER per QALY gained
Carrato et al (2015)[49]	Spain	Nab-Pac+Gem vs Gem	€41,519
Cheng et al (2016)[50]	US	FOLFIRINOX vs Nab-Pac+Gem	$30,870
Cowell et al (2014)[51] [51] [51]	UK	Nab-Pac+Gem vs Gem	£52,885 (no QALY weighting) £37,249 (partial QALY weighting) £21,108 (full QALY weighting)
Fragoulakis et al (2014)[52]	Greece	Nab-Pac+Gem vs Gem	€47,120
Gharaibeh et al (2015)[53]	UK	Nab-Pac+Gem vs Gem	£78,086
Gharaibeh et al (2015)[54]	US	Nab-Pac+Gem vs Gem	$141,338
		FOLFIRINOX vs Gem	$164,495
		Nab-Pac+Gem vs FOLFIRINOX	$37,692
		FOLFIRINOX vs Nab-Pac+Gem	$202,187
Stetka et al (2015)[55]	Slovak Republic	Nab-Pac+Gem vs Gem	€27,769
NICE TA360 (2015)[14]	UK (England and Wales)	Nab-Pac+Gem vs Gem	£51,900
		Nab-Pac+Gem vs FOLFIRINOX	Dominated
		Nab-Pac+Gem vs Gem+Cap	£87,084
SMC (no: 968/14)[2]	UK (Scotland)	Nab-Pac+Gem vs Gem	£52,885
AWMSG (no: 1999)[1]	UK (Wales)	Nab-Pac+Gem vs Gem	£53,260
Osterlund et al (2016)[56] [56] [56]	Norway Sweden Finland Denmark	Erlotinib+Gem	€1,232 (cost per month of OS, average of Nordic countries)
		Erlotinib+Gem	€2,103 (cost per month of PFS, average of Nordic countries)
		Nab-Pac+Gem	€2,602 (cost per month of PFS, average of Nordic countries)

AWMSG=All Wales Medical Strategy Group; ICER=incremental cost effectiveness ratio; OS=overall survival; PFS=progression-free survival; QALY=quality adjusted life year; SMC=Scottish Medicines Consortium; TA=technology appraisal
Source: CS, Table 33

5.3 ERG critique of the company's review of cost effectiveness evidence

The company adequately describes the search strategies used to identify relevant studies related to the use of Nab-Pac+Gem for the treatment of patients with untreated metastatic

pancreatic cancer. The search strategies were originally run in March 2013 and then updated in March 2014 and July 2016. Considering the date of the last update search, there is a chance that relevant papers have not been picked up. Separate searches were conducted for the retrieval of cost effectiveness studies and HRQoL studies. The dates of the searches and the full date spans are included in the CS.

Full details of the separate search strategies used to locate cost effectiveness evidence and HRQoL evidence are reported in Section 5.1 and Appendix 11 of the CS. Both of the search strategies included population terms as well as indication terms and use MeSH and free text. The separate search strategies include a cost effectiveness filter and HRQoL search filter. The ERG considers the search terms used in the strategy and the use of the search filters to be appropriate.

Summary of searching

In summary, the ERG concludes that the company's cost effectiveness and HRQoL search strategies are appropriate and comprehensive enough to identify relevant studies as described in the final scope issued by NICE. However, given that the searches are slightly out of date, it is possible relevant studies may have been missed.

5.4 Summary and critique of the company's submitted economic evaluation by the ERG

The base-case cost effectiveness evaluation undertaken by the company compares the costs and benefits (in terms of QALYs) of treatment with Nab-Pac+Gem versus treatment with Gem in patients with previously untreated metastatic pancreatic cancer. The company also provides scenario analyses comparing the costs and benefits of treatment with Nab-Pac+Gem versus treatment with Gem+Cap, and treatment with Nab-Pac+Gem versus FOLFIRINOX.

5.4.1 Model structure

The company has adapted the model submitted within the original submission to NICE for appraisal TA360[14] rather than constructing a de novo economic model. The company uses a Markov structure in the model and employs an area under the curve approach to estimate the proportion of patients who transition between health states over time from the start of treatment until death. There are three primary health states in the model: pre-progression, post-progression and death. The company has divided the pre-progression state into two secondary health states (pre-progression: on first-line treatment and pre-progression: off first-line treatment) to more accurately estimate drug costs in cases where treatment is discontinued before progression. The company has also included a tunnel state at 4 weeks

to death to account for a period of intensive palliative care in the final stages of life (Figure 5).

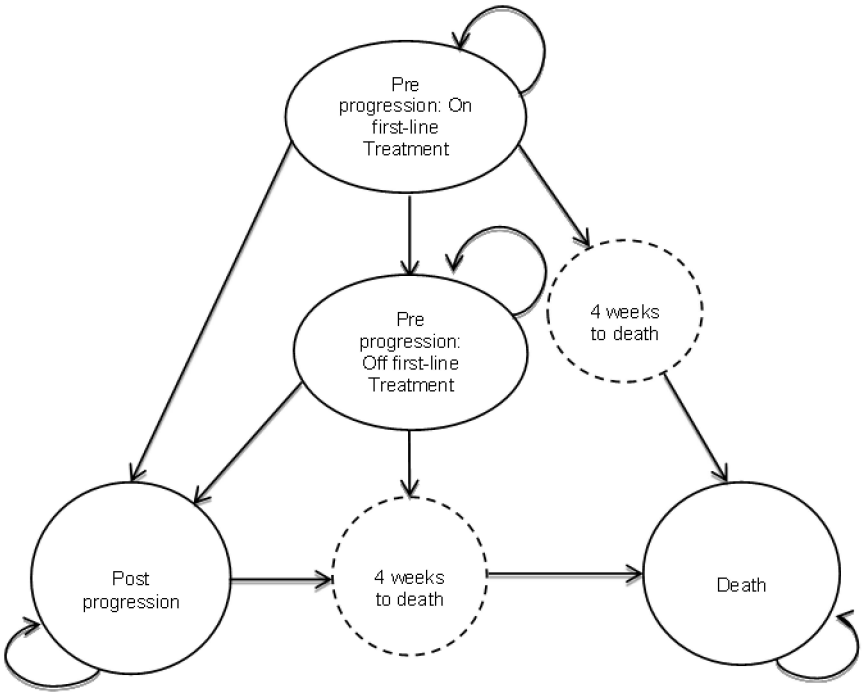

Figure 5 Model schematic

Source: CS, Figure 21

All patients enter the model in the 'pre-progression: on first-line treatment' health state and remain there for one cycle. Patients can then either stay in their current health state or transition to a worse health state at the beginning of each subsequent model cycle. Patients receive second-line treatments on progression. Transition probabilities between health states are informed by survival models fitted to OS, PFS and TOT K-M data from the CA046 trial.

The model cycle length is 1 week and no half-cycle correction has been applied, as the company notes that all drug and administration costs are incurred at the beginning of a cycle, and that using a half-cycle correction has a negligible impact on the ICER per QALY gained.

5.4.2 Population

The population reflected in the company model is adults with untreated metastatic cancer of the pancreas.

5.4.3 Interventions and comparators

Intervention

Nab-Pac is supplied as a powder for intravenous infusion and Gem is supplied as a solution for intravenous infusion. In line with the EMA marketing authorisation[9] for Nab-Pac, Nab-Pac (125mg/m^2) and Gem (1000mg/m^2) are administered sequentially for 30 minutes each on days 1, 8 and 15 of each 28-day cycle until disease progression or unacceptable toxicity.

Comparators

The final scope issued by NICE states that the comparators for this appraisal are Gem, Gem+Cap and FOLFIRINOX. The company considers Gem as the main comparator to Nab-Pac+Gem in the economic analysis with Gem+Cap and FOLFIRINOX considered only as secondary comparators due to a limited evidence base for these treatments in a UK clinical setting. Further details of the comparators are presented in Table 9 of the ERG report.

Second-line treatment

Data describing the seven most prevalent second-line treatments reported in the CA046 trial are used to estimate the range and use of second-line treatments in the model. The percentage of patients receiving second-line therapy in the CA046 trial differed according to study arm: 38% of patients who received Nab-Pac+Gem as a first-line treatment received a second-line treatment and 42% of patients who received Gem as a first-line treatment received a second-line treatment.[12] The proportions of each of the second-line treatments used in the model are shown in Table 27.

Table 27 Second-line treatments included in the company model

Second-line treatment	% of patients moving into second-line treatment	
	Nab-Pac+Gem (total=38%*)	Gem (total=42%)
5-FU	7.3%	1.3%
5-FU+oxaliplatin	13.2%	17.1%
Gem+Cap	2.9%	3.9%
Capecitabine	4.4%	6.6%
Gem+erlotinib	2.9%	3.9%
Erlotinib	1.5%	1.3%
FOLFIRINOX	0.0%	0.0%

5-FU=5-fluorouracil
* The figures do not sum to 38% due to rounding
Source: CS, Table 36

5.4.4 Perspective, time horizon and discounting

The company states that the economic evaluation was undertaken from the perspective of the NHS and PSS (Personal Social Services). The model time horizon was 10 years. Both costs and benefits were discounted at a rate of 3.5% per annum.

5.4.5 Treatment effectiveness and extrapolation

Nab-Pac+Gem and Gem

The company used K-M data from the CA046 trial as a basis for extrapolating survival for treatment with Nab-Pac+Gem and Gem. The company assessed the applicability of a single parametric model or a Cox PH model by visual inspection of the K-M curves, log cumulative hazard plots (LCHP) and quantile-quantile (Q-Q) plots. Six parametric distributions (exponential, log-normal, log-logistic, Gompertz, gamma and Weibull) were examined for each clinical outcome (OS, PFS and TOT). A single stratified approach was considered if a pooled model was deemed inappropriate due to non-PHs or poor visual fit. The company explored the fit of each parametric model using visual inspection, LCHP, Q-Q plots, Akaike information criterion (AIC) and Bayesian information criterion (BIC) goodness of fit statistics, and clinical plausibility.

The company concluded from examination of the LCHP curves that the PH assumption does not hold for OS, PFS or TOT in the CA046 trial; for each of these outcomes the LCHP curves cross. The company thus considered stratified versions of the six parametric models to allow for a more flexible approach to extrapolation. For OS, PFS and TOT, the stratified gamma model was considered to be the most appropriate choice as these curves had the lowest AIC/BIC and, according to the company, provided a good fit to the observed dataset. For OS and PFS, as the unstratified gamma curves also yielded plausible values and, according to the company, provided a good fit to the observed dataset and so use of the unstratified gamma model was considered in the scenario analyses conducted by the company. Use of the ERG's curves that were submitted during the earlier appraisal (TA360[14]) were also included as scenario analyses.

Gem+Cap and FOLFIRINOX

The company updated the NMA undertaken for TA360[14] to incorporate any clinical evidence that had become available since the original submission. Hazard ratios for treatment with Nab-Pac+Gem versus Gem+Cap or FOLFIRINOX from the updated NMA were used to model OS and PFS in the cost effectiveness model for Nab-PAC+Gem versus these two comparators. The company notes (CS, p160) …'that due to the lack of support for the assumption of PHs in the OS and PFS data from the CA046 trial, the PH assumption underpinning the NMA is questionable and therefore the comparison between Nab-Pac+Gem and Gem+Cap or FOLFIRINOX is questionable.'

5.4.6 Health-related quality of life

No HRQoL data were collected during the CA046 trial. The company updated the search for HRQoL data from the previous NICE submission (TA360) to ensure that the latest available data are presented in the CS. Details of the searches are given in Section 5.4.1 of the CS. The company also analysed HRQoL data from the Phase II SIEGE trial.[28] Three sets of health state utility values were considered by the company for use in the cost effectiveness model: two[57,58] from the SIEGE trial[28] and one from a paper by Romanus et al.[59]

The SIEGE trial[28] was designed to investigate the clinical effectiveness of two different dosing regimens for Nab-Pac+Gem, one of which matched the regimen used in the CA046 trial. The company derived utility values from answers to the EQ-5D-5L questionnaire; trial participants completed questionnaires at baseline, at 4-weekly intervals during pre-progression and at 12-weekly intervals during post-progression over a period of 12 months.

Two distinct methods were used to derive utility values from the collected data from patients in the SIEGE trial:[28] first, using the EQ-5D-5L value set published by Devlin et al;[57] and second, using the 'crosswalk method'[58] which allows EQ-5D-3L utility values to be generated from EQ-5D-5L data.

The company explains (CS, p184) that multivariate regression analysis was conducted to determine the most significant predictors of HRQoL over time; only progression status and KPS (KPS≤80 and KPS>80 based on clinical evidence from the CA046 trial CSR) were included in the final multivariate models. The results of the regression analysis were combined with the results generated by applying the Devlin[57] and crosswalk[58] methods to produce two sets of utility value estimates from the SIEGE trial[28] data (Table 28).

The company also considered the findings from a study by Romanus.[59] This RCT compared Gem+bevacizumab versus Gem+placebo in US patients via telephone interviews with advanced pancreatic cancer using the EQ-5D at baseline and at 8 weeks. The company has applied an (unexplained) adjustment to the values reported in the publication to represent a UK, rather than US, population (Table 28); the adjustment was made in line with the ERG feedback from the original NICE submission (TA360[14]).

Table 28 Health state utility values

	Health state utility	
	Pre-progression	**Post-progression**
Devlin57 value set (SIEGE)	0.79	0.75
Crosswalk method58 (SIEGE)	0.70	0.65
Romanus et al (2012)59 with UK adjustment	0.74	0.67

Source: CS, Table 52

The company notes that there is substantial uncertainty in the utility values derived from the SIEGE trial[28] depending on the method of analysis used. As the results from the Romanus[59] paper lie between the two sets of values derived from the HRQoL data collected in the SIEGE trial,[28] the company has used the Romanus[59] values in the base-case analysis and the values derived from the SIEGE trial data in the scenario analyses. The company acknowledges that all three approaches have strengths and weaknesses (not least that the adjusted utility values from the Romanus[59] paper are not specific to patients receiving Nab-Pac+Gem).

Baseline health state utility values were assumed to be the same for all patients irrespective of treatment. However, these values were then retrospectively adjusted to reflect the AE profiles of the treatments.

5.4.7 Adverse events

The company model includes AEs recorded during the CA046 trial that met the following criteria: treatment emergent; Grade ≥3; or occur in >5% of patients in either arm. Clinicians were consulted about any AEs that met the first two criteria but were present in <5% of patients in the CA046 trial. The purpose of this consultation was to identify any AEs that would have a substantial impact on HRQoL or on resource use and costs. In total, 19 AEs were identified that met the inclusion criteria.

The probability of an AE occurring was calculated based on incidence and mean length of exposure to treatment data collected in the CA046 trial. The rates of AEs for patients treated with Nab-Pac+Gem and Gem were taken from the CA046 trial. The rates of AEs for Gem+Cap were assumed to be the same as for patients treated with Nab-Pac+Gem.

The rates of AEs for patients treated with FOLFIRINOX were calculated as relative risks (RRs) compared with rates for patients treated with Gem, which were extracted from a published source,[7] which were then applied to the Gem AE data from the CA046 trial. For AEs where data were not reported, AE rates and durations were assumed to be the same as for Nab-Pac+Gem.

5.4.8 Resources and costs

The company did not present any treatment-specific resource use literature in the CS for TA360.[14] Instead, the company estimated resource use (as part of follow-up and monitoring) through clinician interviews and a panel of experts validated these estimates at a UK advisory board meeting. In the current submission, the company adopts the same approach.

Drug acquisition costs

The drug acquisition costs for first-line treatments are presented in Table 29. The list price for Nab-Pac is £246.00 per vial, which is reduced to [redacted] per mg with the application of a PAS.

Table 29 Drug acquisition costs

Treatment	Unit cost including PAS	Unit price per mg	Weighted unit price per mg	Source
				Gemcitabine
1g powder for solution for infusion vials	£30.89	£0.03	£0.03	eMIT.[60] Date accessed: 19 January 2017
200mg powder for solution for infusion vials	£3.99	£0.02		
Nab-Paclitaxel				
Powder for reconstitution, paclitaxel, net price 100-mg vial	[redacted]	[redacted]	[redacted]	MIMS.[61] Data accessed: 19 January 2017
Capecitabine				
150mg, 60-tab pack	£7.73	£0.0009	£0.001*	eMIT.[60] Date accessed: 19 January 2017
500mg, 120-tab pack	£29.59	£0.0005		
Erlotinib				
25mg, 30-tab pack	£378.33	£0.50	£0.44	MIMS.[61] Data accessed: 19 January 2017
100mg, 30-tab pack	£1,324.14	£0.44		
150mg, 30-tab pack	£1,631.53	£0.36		
5-fluorouracil bolus injection				
1g/20ml (5%) solution for injection vials	£4.00	£0.02	£0.01	BNF January 2017[62]
500mg/10ml (5%) solution for injection vials/Pack size 1	£6.40	£0.01		
Oxaliplatin				
100mg/20ml solution for infusion vials	£15.50	£0.16	£0.17	eMIT.[60] Date accessed: 19 January 2017
50mg/10ml solution for infusion vials	£10.62	£0.21		
5-fluorouracil Infusion				
2.5g/50ml (5%) solution for infusion vials	£4.68	£0.002	£0.004*	eMIT.[60] Date accessed: 19 January 2017
5g/100ml (5%) solution for infusion vials	£4.53	£0.001		
Folinic acid (Leucovorin®)				
Calcium folinate 100mg/10ml solution for injection vials/Pack	£2.29	£0.02	£0.02	eMIT.[60] Date accessed: 19 January 2017
Calcium folinate 300mg/30ml solution for injection vials/ Pack	£4.59	£0.02		
Irinotecan				
100mg/5ml solution for infusion vials/Pack size 1	£7.52	£0.08	£0.07	eMIT.[60] Date accessed: 19 January 2017
300mg/15ml solution for infusion vials/Pack size 1	£18.64	£0.06		

BNF=British National Formulary; eMIT=electronic market information tool; MIMS=Monthly Index of Medical Specialties
*Less than 1p per mg
Source: CS, Table 57

Second-line drug costs

In the absence of data detailing dosing regimens for second-line chemotherapy treatments (see Table 27), the company has assumed that dosing in the second-line setting is the same as dosing in the first-line setting.

Dosing

Dosing information for treatment with Nab-Pac+Gem and Gem was obtained from the CA046 trial as reported in the publication by Von Hoff.[12] Dosing information for Gem+Cap and FOLFIRINOX (ACCORD study) were obtained from published sources.[4,7]

Doses for all drugs (with the exception of capecitabine and erlotinib) are based on a patient's body surface area (BSA). The average BSA used in the cost effectiveness model is 1.75m^2, which was taken from the KANTAR study for the UK pancreatic cancer population.[15]

For full information on individual doses for the drugs, see Table 9 of this ERG report.

Vial sharing

Vial sharing is not included in the base-case analysis, but is investigated as a scenario analysis.

Dose intensity and missed doses

The company base-case analysis includes adjustments to the cost of each first-line treatment to take into account any cost-saving effect of reduced or missed doses. Data from the CA046 trial were used to inform the proportion of reduced or missed doses applied in the model. The proportions of reduced or missed doses that could be anticipated (and therefore would not lead to drug wastage) were estimated based on the results (n=26) of a survey of waste management procedures in hospital pharmacies, and of waste management procedures associated with Nab-Pac dose modification/adjustment and dose cessation in the UK. Clinical experts validated the survey results.

Half of the survey respondents stated that they had pre-specified waste management policies in place to avoid drug wastage (e.g., drug preparation on day of treatment, not preparing drugs until blood results were received). The company used these responses to inform the modelling assumption that 50% of first-time dose reductions and 50% of missed doses could be anticipated. The company has assumed that all subsequent dose reductions could be anticipated and would, therefore, not result in wastage. The adjustments were applied to patient level data for patients missing a Nab-Pac dose, Gem dose or both.

The average dose intensity used in the model to estimate the cost of reduced doses is 89.83%, weighted to include the 79.7% of subsequent doses (assumed 100% anticipated) and 20.3% of first-time reductions (assumed 50% anticipated).

The proportion of anticipated dose reductions and missed doses for patients receiving Gem+Cap and FOLFIRINOX were assumed to be the same as for patients receiving Nab-Pac. The assumption that no missed or reduced doses can be anticipated (and, therefore, no cost savings accrued) is explored in a scenario analysis.

Administration costs

The company has used NHS Reference Costs (2015/16)[63] and Personal Social Services Research Unit (PSSRU) costs (2016)[64] as estimates for the cost of administering chemotherapy. Table 30 shows the costs of administration associated with each first-line treatment.

Table 30 Administration costs of chemotherapy treatments

Chemotherapy	Component drug name	Administration cost	Source	Total cost per treatment
Gem	Gem	£253.32	NHS Reference Cost[63] SB12Z	£253.32
Nab-Pac	Nab-Pac	£17.50	PSSRU (day ward nurse)[64]	£270.83
	Gem	£253.32	NHS Reference Cost[63]SB12Z	
Gem+Cap	Gem	£253.32	NHS Reference Cost[63] SB12Z	
	Cap	£0	-	£253.32
FOLFIRINOX	Oxaliplatin	£336.57	NHS Reference Cost[63] SB13Z	£506.54
	Irinotecan	£17.50	PSSRU (day ward nurse)[64]	
	5-FU	£17.50	PSSRU (day ward nurse)[64]	
	Folinic acid	£17.50	PSSRU (day ward nurse)[64]	
	5-FU continuous infusion	£117.47	PSSRU (day ward nurse)[64] + NHS Reference Cost[63]	

PSSR=Personal Social Services Research Unit
Source: CS, Table 61

An extra 30 minutes pharmacy time is also included in the administration costs for Nab-Pac as the drug has to be reconstituted from powder, which takes longer to prepare than other infusions. Preparation of Nab-Pac also requires a 15-micron filter at a cost of £2.04.

Monitoring costs

Monitoring costs were applied in the 'pre-progression: on first-line treatment' health state and in the post-progression health state for those patients receiving second-line treatment. Monitoring costs for patients receiving active treatment are categorised as either first-line (immediately prior to initiation of chemotherapy), and first- and second-line (follow-up and monitoring).

First-line costs prior to chemotherapy are £325.37 for all treatments except FOLFIRINOX, which costs £369.35 due to additional requirement for ECG and echocardiogram. Weekly follow-up and monitoring costs in first- and second-line are £87.52 for all treatments except FOLFIRINOX, which costs £175.03. Patients treated with FOLFIRINOX are assumed to be monitored twice as often as patients receiving other treatments as the treatment is assumed to be more toxic.

Details of the individual elements of monitoring costs can be found in the company model (1^{st}_Line_Costs and 2^{nd}_Line_Costs), as Table 64 in the CS contains errors that lead to an underestimate of the total costs by £18.26.

Palliative care costs

Patients in the 'pre-progression: off first-line treatment' health state in the model were assumed to receive monitoring that was costed as palliative care provided by one GP home visit per week (at a cost of £31). However, in the CS (p207), the company states that these patients receive one nurse visit per week at a cost of £44, but this is an error as it is not borne out by the model. Patients who do not receive second-line treatment are also assumed to receive palliative care provided by one GP home visit per week.

G-CSF

The company states that G-CSF use in the CA046 trial was higher than would be expected in clinical practice (see Table 31 for details). However, because the estimated survival benefits of treatment with Nab-Pac+Gem are taken directly from the CA046 trial and used in the company model, it was deemed appropriate to include G-CSF use for patients treated with Nab-Pab+Gem and patients treated with Gem according to the CA046 trial data. The company considers G-CSF use according to current practice in a scenario analysis.

Table 31 G-CSF usage in the CA046 trial and in clinical practice

	Number of patients treated (CA046 trial)		**Cycle probability**		**Average cost per treatment**		**Average cost per cycle**	
	NPG	Gem	NPG	Gem	NPG	Gem	NPG	Gem
G-CSF treatment according to trial data	110	63	0.012	0.010	£191.04	£191.04	£2.33	£0.40
G-CSF treatment for febrile neutropenia (clinical practice)	14	6	0.002	0.001	£584.91	£477.12	£1.05	£0.50

NPG=Nab-Pac+Gem
Source: CS, Table 66

Due to the absence of any clinical data, the use of G-CSF by patients treated with Gem+Cap was assumed to be the same as for patients treated with Nab-Pac+Gem. G-CSF use by patients treated with FOLFIRINOX was taken from the ACCORD trial.[34]

Adverse events costs

The cost of AEs was included in the model as the cycle probability of an event occurring, multiplied by the cost of that event. Costs for AEs were taken from NHS Reference Costs (2015/16)[63] and validated by clinicians and are shown in Table 32.

Table 32 Adverse event costs

Grade 3+ TEAEs	Cost	NHS Reference Cost 2015/16[63] description
Neutropenia	£97.29	HRG code: XD25Z Neutropenia drugs band 1, NHS Trusts High Cost Drugs: Admitted Patient Care
Fatigue*	£35.00	Assumption: Fatigue assumed as one nurse visit per day of fatigue
Thrombocytopenia	£498.81	HRG code SA12K, Thrombocytopenia with CC Score 0-1 non-elective inpatients (short-stay)
Anaemia	£481.06	HRG code SA04L, Iron Deficiency Anaemia with CC Score 0-1, Non-elective short stay
Leukopenia	£97.29	No specific data available – assumed to be equal to neutropenia
Peripheral sensory neuropathy (pain)	£139.12	HRG code: 191 NHS Reference Costs 2015/2016 Total outpatient procedures, pain management
Neuropathy peripheral (pain)	£139.12	HRG code: 191 NHS Reference Costs 2015/2016 Total outpatient procedures, pain management
Dehydration	£808.64	HRG code: KC05H, Fluid and Electrolyte Disorders, with Interventions, with CC Score 0-4, Non-elective inpatient short stay
Asthenia*	£35.00	Assumption: Asthenia assumed as one nurse visit per day of asthenia
Abdominal pain	£1,124.81	HRG Code: FZ90A, Abdominal Pain with Interventions, non-elective in patient (short stay)
Nausea***	£379.38	Assumption: same as diarrhoea
Diarrhoea	£379.38	HRG code FZ91M, Non-Malignant Gastrointestinal Tract Disorders without Interventions, with CC Score 0-2, day case
Vomiting***	£379.38	Assumption: same as diarrhoea
Decreased appetite***	£379.38	Assumption: same as diarrhoea
Pulmonary embolism	£1,549.87	HRG code DZ09K: Pulmonary Embolus with Interventions, with CC Score 0-8, non-elective inpatient
Pneumonia	£1,984.07	HRG code: DZ19L, Other Respiratory Disorders without Interventions, with CC Score 11+, Non- elective inpatient long stay
Febrile Neutropenia**	£2,067.07	HRG Code: SA08J, Other Haematological or Splenic Disorders, with CC Score 0-2, non-elective inpatient
Cholangitis	£1,530.00	Assumption: UK Advisory board estimate 5 x cost of 1 excess bed day from NHS reference manual 2015/2016
Hyperbilirubinemia***	£435.22	Assumption: UK Advisory board: 1 consultant visit, 5 community nurse visits plus 1 ultrasound

CC=complexity and comorbidity; G-CSF=granulocyte colony-stimulating factor; HRG=Healthcare Resource Group; NHS=National Health Service; TEAE=treatment-emergent adverse event
* Cost shown is unit cost of 1-hour community nurse time, unit cost multiplied by duration of fatigue on each arm before application to model; ** Patients with febrile neutropenia treated with G-CSF from the start of the adverse event to the end of chemotherapy treatment. This cost is applied in addition to the HRG code (SA08F) and is not shown here – see Section 5.1 of the CS; *** Based on clinical opinion from recent UK advisory board
Source: CS, Table 68

Terminal care costs

An additional tunnel state of '4 weeks to death' is included in the model for the estimation of terminal care costs. In the base-case analysis, terminal care costs have been calculated based on a micro-costing approach that considers the cost of dying in hospital, at a hospice or at home, and weights these estimates based on the proportion of patients considered to die in each of these settings (Table 33). Full details of this approach are presented in Section 5.5.5 of the CS.

Table 33 Terminal care costs

	Proportion*	Total weekly cost	Weighted weekly cost
Death in hospital	56%	£929	£518
Death in hospice	17%	£1,137	£192
Death at home	27%	£1,274	£348
Total weighted weekly cost:			£1,058

*Proportions are taken from the ERG report in TA360[14]
Source: CS, Table 69

The company carried out two scenario analyses that model End of Life costs as per the company's original submission for TA360,[14] and as per an estimate of £6,153 for the last 8 weeks of life as modelled by the King's Fund.[65] These results are shown in Table 38.

5.4.9 Cost effectiveness results (PAS price)

The results presented in Section 5.4.9 to Section 5.4.12 are taken directly from the CS. However, the company updated the economic model during the clarification period. The **updated** incremental cost effectiveness ratio (ICER) per QALY gained (£46,932) for Nab-Pac+Gem versus Gem is slightly higher than the submitted base-case ICER per QALY gained (£46,657) for Nab-Pac+Gem versus Gem that is reported in the CS.

All of the company's cost effectiveness results are based on the PAS price of Nab-Pac. However, the company states (CS, p242) that the non-PAS ICER for Nab-PAC+Gem is £[redacted] per QALY gained. No further mention of this non-PAS ICER is made in the CS.

The base-case cost effectiveness results generated by the company's model are shown in Table 34. In the base-case analysis, treatment with Nab-Pac+Gem generates more benefits than treatment with Gem (+0.202 life years and +0.144 QALYs) at an increased cost (+£6,717). The company base-case ICER for the comparison of treatment with Nab-Pac+Gem versus Gem is £46,657 per QALY gained. Full details of the disaggregated results are presented in Section 5.7.3 of the CS.

Table 34 Base-case cost effectiveness results

Technologies	Total costs	Total LYG	Total QALYs	Inc. costs	Inc. LYG	Inc. QALYs	ICER per QALY gained
Gem	[redacted]	0.725	0.396				
Nab-Pac+Gem	[redacted]	0.927	0.540	£6,717	0.202	0.144	£46,657

ICER=incremental cost effectiveness ratio; LYG=life years gained; QALYs=quality adjusted life years; Inc=incremental
Source: CS, Table 71

The results of the company's cost effectiveness analysis for the comparison of treatment with Nab-Pac+Gem versus Gem+Cap and versus FOLFIRINOX are given in Table 35 and Table 36. These comparisons are described as scenario analyses in the CS.

Treatment with Nab-Pac+Gem generates fewer benefits than treatment with Gem+Cap (-0.02 life years and -0.01 QALYs) at an increased cost (+£5,555). When compared to treatment with Gem+Cap, treatment with Nab-Pac+Gem is dominated (i.e., is more expensive and less effective).

Table 35 Company's cost effectiveness results for treatment with Nab-Pac+Gem vs Gem+Cap

Technology	Total costs	Total LYG	Total QALYs	Inc. costs	Inc. LYG	Inc. QALYs	ICER per QALY gained
Gem+Cap	[redacted]	0.95	0.55				
Nab-Pac+Gem	[redacted]	0.93	0.54	+£5,555	-0.02	-0.01	Dominated

ICER=incremental cost effectiveness ratio; Inc=incremental; LYG=life years gained; QALYs=quality adjusted life years
Source: CS, adapted from Table 81

Treatment with Nab-Pac+Gem generates fewer benefits than treatment with FOLFIRINOX (-0.22 life years and -0.015 QALYs) at an increased cost (+£1,543). Compared with treatment with FOLFIRINOX, treatment with Nab-Pac+Gem is dominated (i.e., is more costly and less effective).

Table 36 Company's cost effectiveness results for treatment with Nab-Pac+Gem vs FOLFIRINOX

Technology	Total costs	Total LYG	Total QALYs	Inc. costs	Inc. LYG	Inc. QALYs	ICER per QALY gained
FOLFIRINOX	[redacted]	1.15	0.69				
Nab-Pac+Gem	[redacted]	0.93	0.54	+£1,543	-0.22	-0.15	Dominated

ICER=incremental cost effectiveness ratio; Inc=incremental; LYG=life years gained; QALYs=quality adjusted life years
Source: CS, adapted from Table 81

5.4.10 Sensitivity analyses

Deterministic sensitivity analysis

The company performed one-way sensitivity analyses to explore the sensitivity of the cost effectiveness results generated by the model (240 individual inputs were varied). Results from varying the ten most influential parameters are presented in the CS as a tornado diagram, which is reproduced as Figure 6. The results show that the most influential parameters are the treatment variables used to parameterise OS, TOT and PFS.

Figure 6 Results from company's one-way sensitivity analyses

OS=overall survival; PFS=progression-free survival; TOT=time on treatment
Source: CS, Figure 40

Probabilistic sensitivity analysis

The company undertook a probabilistic sensitivity analysis (PSA) to derive the mean ICER per QALY gained for the comparison of the cost effectiveness of treatment with Nab-Pac+Gem versus Gem. The PSA was run for 1000 iterations. Results from the company's base-case deterministic analysis and PSA are shown in Table 37.

Table 37 Base-case deterministic versus PSA cost effectiveness results

	Incremental costs	Incremental QALYs	ICER per QALY gained
Deterministic result	£6,717	0.144	£46,657
Average value from PSA	£6,758	0.140	£46,801

ICER=incremental cost effectiveness ratio; PSA=probabilistic sensitivity analysis; QALY=quality adjusted life year
Source: CS, Table 71 and Table 77

Results from the PSA suggest a [redacted] likelihood of treatment with Nab-Pac+Gem being cost effective versus treatment with Gem at a willingness-to-pay (WTP) threshold of £30,000 per QALY gained and a [redacted] likelihood of treatment with Nab-Pac+Gem being cost effective versus treatment with Gem at a WTP threshold of £50,000 per QALY gained. The results from the PSA are presented as a cost effectiveness plane in Figure 7 and a cost effectiveness acceptability curve in Figure 8.

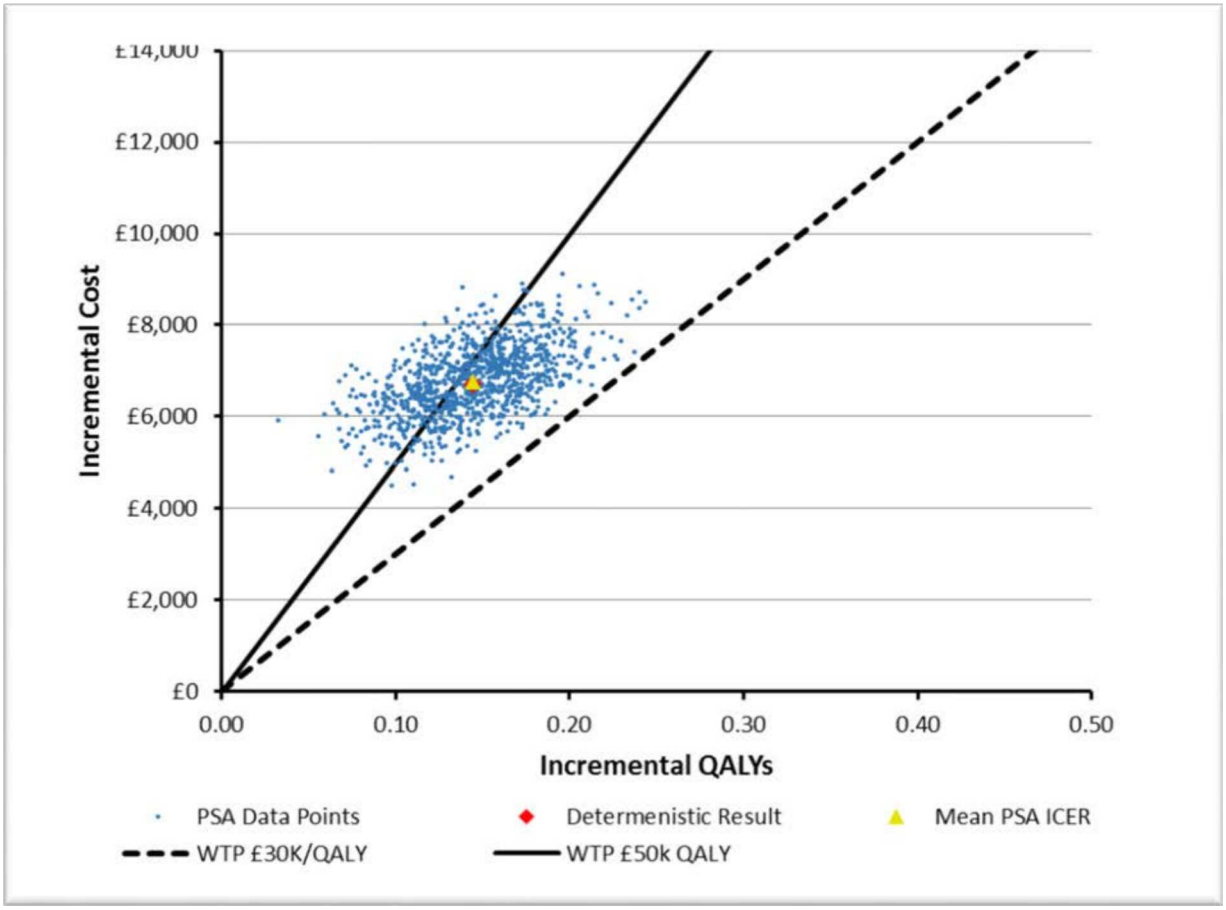

Figure 7 Cost effectiveness plane for treatment with Nab-Pac+Gem vs Gem

Figure 8 Cost effectiveness acceptability curve for treatment with Nab-Pac+Gem vs Gem

Source: CS, Figure 39

5.4.11 Scenario analyses

The company presents the results of 25 scenarios used to explore different structural assumptions for the comparison of treatment with Nab-Pac+Gem versus Gem. The structural scenario with the biggest impact on the ICER per QALY gained is the assumption of no anticipated missed doses. The second most influential change was the use of the ERG OS curve from TA360[14] and the third most influential change was the availability of a 250mg vial for Nab-Pac (Table 38).

Table 38 Structural scenario analyses results (top ten [and End of Life] impact on ICER per QALY gained)

Base case	Scenario	Incremental costs	Incremental QALYs	ICER	Difference from base-case ICER
Base case	-	£6,717	0.14	£46,657	-
Proportion of time missed doses anticipated overall (first and subsequent dose) - 50.00% and 100.00%	0.00% and 0.00%	£7,356	0.14	£51,097	9.52%
Stratified Gamma	ERG curve fits	£7,308	0.15	£50,307	7.82%
250mg vial availability – No 250mg vial	250mg vial	£6,250	0.14	£43,416	-6.95%
Utilities - Romanus	SIEGE Devlin value set (no AE utility decrement)	£6,717	0.15	£43,460	-6.85%
Romanus with AE utility decrements	SIEGE Devlin value set with AE utility decrements	£6,717	0.15	£43,471	-6.83%
Utilities - Romanus	SIEGE crosswalk (no AE utility decrement)	£6,717	0.14	£49,303	5.67%
Assessment of PFS – Investigator assessment	Independent assessment	£6,969	0.14	£48,968	4.95%
Source of BSA data – UK data	Trial based BSA	£7,016	0.14	£48,739	4.46%
Parametric survival curves (OS, PFS, TOT) – Stratified Gamma	Gamma	£6,570	0.14	£46,107	-1.18%
Discount rate (costs and QALYs) - 3.50%	0%	£6,789	0.15	£46,117	-1.16%
Duration of end of life utility decrements and costs applied for – utility decrement: 12 weeks	Utility decrement: 4 weeks	£6,717	0.14	£46,767	0.23%
End of life costs: 4 weeks	End of life costs: 12 weeks	£6,714	0.15	£46,641	-0.03%

AE=adverse event; BSA=body surface area; G-CSF=granulocyte-colony stimulating factor; ICER=incremental cost effectiveness ratio; OS=overall survival; PFS=progression-free survival; QALY=quality adjusted life year; ToT=time on treatment
Source: Adapted from CS, Table 80

The company also considered the comparison of Nab-Pac+Gem versus Gem+Cap and versus FOLFIRINOX to be scenario analysis. The results of these comparisons are presented in Table 35 and Table 36 of this ERG report.

5.4.12 Subgroup analyses

The company did not carry out any cost effectiveness subgroup analyses.

5.4.13 Model validation and face validity check

According to the company (CS, p241) …'The model was quality assured by the internal processes of the external economists who adapted the economic model.' These processes included review of the model for coding errors, inconsistencies and plausibility of inputs. The model was also subject to a checklist[66] of known modelling errors.

The model inputs were also validated by clinical advisory boards and by comparing results from the model with any previously published model estimates[51,67] that were identified by the company's literature search. The publication by Gharaibeh[67] reports an ICER of £78,086 per QALY gained for Nab-PAC+Gem versus Gem, which the company states is similar to the non-PAS ICER of [redacted] per QALY gained that is reported in the CS (p242).

5.5 ERG critique of company's submitted economic evaluation

Table 39 NICE Reference case checklist completed by ERG

Attribute	Reference case	Does the de novo economic evaluation match the reference case?
Decision problem	The scope developed by the Institute	Yes, although two of the comparators in the final scope are not considered in the company's base case analysis
Comparator(s)	Alternative therapies routinely used in the NHS	Yes
Perspective costs	NHS and PSS	PSS costs were not fully considered in the CS
Perspective benefits	All health effects on individuals	Yes
Form of economic evaluation	Cost effectiveness analysis	Yes
Time horizon	Sufficient to capture differences in costs and outcomes	Yes
Synthesis of evidence on outcomes	Systematic review	Yes, for OS and PFS for treatment with Gem+Cap and FOLFIRINOX, and for HRQoL outcomes
Outcome measure	Quality adjusted life years	Yes
Health states for QALY	Described using a standard and validated instrument	Yes
Benefit valuation	Time-trade off or standard gamble	Yes
Source of preference data for valuation of changes in HRQoL	Representative sample of the public	Yes
Discount rate	An annual rate of 3.5% on both costs and health effects	Yes
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes
Sensitivity analysis	Probabilistic sensitivity analysis	Yes

EQ-5D=EuroQol-5 dimension; QALY=quality adjusted life year; HRQoL=health-related quality of life; OS=overall survival; PFS=progression-free survival: PSS=Personal Social Services; CS= company submission

Table 40 Critical appraisal checklist for the economic analysis completed by the ERG

Question	Critical appraisal	ERG comment
Was a well-defined question posed in answerable form?	Yes	
Was a comprehensive description of the competing alternatives given?	Yes	
Was the effectiveness of the programme or services established?	Partly	Effectiveness for treatment with Nab-Pac+Gem versus Gem+Cap and versus FOLFIRINOX not robustly established due to issues with the NMA
Were all the important and relevant costs and consequences for each alternative identified?	Yes	
Were costs and consequences measured accurately in appropriate physical units?	Partly	Error in the calculation of total LY and QALYs
Were the cost and consequences valued credibly?	Partly	Drug cost calculations did not take into account all available vial sizes
Were costs and consequences adjusted for differential timing?	Yes	
Was an incremental analysis of costs and consequences of alternatives performed?	Yes	
Was allowance made for uncertainty in the estimates of costs and consequences?	Yes	
Did the presentation and discussion of study results include all issues of concern to users?	Yes	

LY=life year; QALY=quality adjusted life year

The company's Microsoft Excel spreadsheet model is constructed according to conventional practice and is generally implemented correctly. The company provided two models as part of its submission: an original model, the results of which are given in the CS; and an updated model corrected for AE calculations, which was provided during the clarification process. The ERG has used the updated model as the basis for its critique and revisions. The original base case ICERs per QALY gained are presented in Table 46 (Nab-Pac+Gem versus Gem), Table 47 (Nab-Pac+Gem versus Gem+Cap), and Table 48 (Nab-Pac+Gem versus FOLFIRINOX) alongside the company's updated base case and the ERG's revisions.

5.5.1 ERG corrections

Application of HRs for treatment with Gem+Cap and FOLFIRINOX

The implementation of the company's estimates of OS, PFS and TOT for treatment with Gem+Cap and with FOLFIRINOX is incorrect. The company uses HRs from the NMA to estimate the relative treatment effect for Nab-Pac+Gem versus Gem+Cap or FOLFIRINOX and applies these treatment effects by raising each cycle probability for OS, PFS and TOT to the power of the relevant HR. However, the HR does not function as a multiplier in this way.

The HR should instead be applied to the treatment parameter within the definition of the curve.

The ERG has corrected the application of the HRs within the company model. Applying the ERG's correction to the modelling of time-to-event outcomes for treatment with Gem+Cap and with FOLFIRINOX

Total life year and QALY calculations

The company's area under the curve estimations of total QALYs and LYs are slightly overestimated, as they include a value for the first cycle. No QALYs or LYs should be accrued at the very beginning of the very first cycle, as patients have only just entered the model. However, it is correct that costs are accrued in the first cycle, as it is assumed that treatment is received on Day 1 of a cycle.

The ERG has corrected the calculation of total QALYs and life years so that accrual begins in the second cycle of the model. Applying the ERG's correction to the calculation of total QALYs and LYs increases the ICER per QALY gained for the comparison of treatment with Nab-Pac+Gem versus Gem by £79 to £47,011. Treatment both with Gem+Cap and with FOLFIRINOX continue to dominate treatment with Nab-Pac+Gem.

All ICERs per QALY gained in the ERG's critique are quoted with reference to the ERG's corrected company base case for each comparator (Nab-Pac+Gem versus Gem=£47,011, Nab-Pac+Gem versus Gem+Cap=Dominated, Nab-Pac+Gem versus

FOLFIRINOX=Dominated).

5.5.2 Major issues

Comparators

The final scope issued by NICE for this appraisal indicates that, for treatment with Nab-Pac+Gem, there are three appropriate comparators: Gem, Gem+Cap, and FOLFIRINOX. Evidence of relative clinical effectiveness for Nab-Pac+Gem, Gem+Cap and FOLFIRINOX compared with Gem is provided by data from three clinical trials.

The company argues for restricting consideration to the comparison of Nab-Pac+Gem versus Gem on the basis that there is a distinct subgroup of patients with metastatic adenocarcinoma of the pancreas currently receiving Gem who are most likely to be suitable for transfer to the Nab-Pac+Gem regimen. On this basis, the company base-case analysis is restricted to the analysis of evidence from the CA046 trial. This subgroup makes up approximately [redacted] of patients currently receiving treatment. The company does not

describe the characteristics of these patients for whom clinical effectiveness has been assessed.

For completeness, the company presents the results of a wider set of cost effectiveness analyses (CS, Table 81); Gem+Cap and FOLFIRINOX were considered to be comparators in separate scenario analyses. From this it can be deduced that the results of pair-wise comparisons of Nab-Pac+Gem versus Gem+Cap, and versus FOLFIRINOX indicate that Nab-Pac+Gem is dominated by both of these comparators, exhibiting inferior outcomes (incremental LYs and incremental QALYs per patient) as well as incurring higher costs per patient (Table 41).

Table 41 Company cost effectiveness results for Nab-Pac+Gem vs Gem-Cap and FOLFIRINOX

Treatment	Incremental costs	Incremental QALYs	ICER
Gem+Cap	[redacted]	-0.011	Dominated
FOLFIRINOX	[redacted]	-0.153	Dominated

Source: Updated company model

The comparison of treatment with Nab-Pac+Gem versus Gem uses modelled parametric curves based on data from the CA046 trial that do not rely on the PH assumption nor the results from the NMA.

However, the company applies HRs from the NMA to the OS and PFS estimates for treatment with Nab-Pac+Gem in order to create estimates of OS and PFS for treatment with Gem+Cap and FOLFIRINOX. This approach is not valid, as it relies on the PH assumption holding between treatment with Nab-Pac+Gem versus Gem in the CA046 trial when PH is shown to be violated in this trial (Section 4.2.4). The ERG is also concerned that the company's application of a HR is inappropriate. The ERG has used the company's approach to fitting an HR to the stratified Gamma model due to the limitations of the model; however, it urges that the results be interpreted with caution.

If PH can be shown to hold for treatment with Gem+Cap versus Gem and FOLFIRINOX versus Gem, then HRs could be applied to OS and PFS estimates for treatment with Gem from the CA046 trial to create estimates of OS and PFS for treatment with Gem+Cap and FOLFIRINOX. The ERG's approach to applying comparator HRs to the model is outlined in Appendix 10.10 of this ERG report. The ERG investigated whether the PH assumption holds in the two trials[6,7] included in the SA2 reduced network NMA (Section 4.6.6).

For treatment with Gem+Cap versus Gem, the ERG found that, given the limited data available, the PH assumption was not strongly violated for either OS or PFS. For treatment

with FOLFIRINOX versus Gem, it found the PH assumption to be strongly violated for both OS and PFS. The results of the ERG's PH tests are given in Appendix 10.11.

The ERG has provided cost effectiveness results from the model for treatment with Gem+Cap and with FOLFIRINOX (using published HRs versus treatment with Gem) for completeness and to provide a sensitivity analysis versus the company's base case using HRs from the NMA. However, these results should be treated with caution, as they apply a HR to a stratified Gamma model, which is not appropriate.

The ERG has applied the HRs shown in Table 42 to model estimates of OS and PFS for treatment with Gem (and assumed that the HRs for PFS also apply to TOT).

Table 42 HRs used in ERG amended model

Comparator vs Gem	Source	HR
Gem+Cap OS	Scheithauer 2003[6]	0.82
Gem+Cap PFS	Scheithauer 2003[6]	0.81
FOLFIRINOX OS	Conroy 2011[7]	0.57
FOLFIRINOX PFS	Conroy 2011[7]	0.47

Source: Figure 9 and Figure 10, CS Appendix 4;

The ERG's analysis generates a mean OS gain of 0.8 months and a mean PFS gain of 1.18 months for treatment with Nab-Pac+Gem generates versus Gem+Cap. Treatment with Gem+Cap no longer dominates treatment with Nab-Pac+Gem once the ERG's revised HRs are applied, as treatment with Nab-Pac+Gem shows increased benefit over Gem+Cap (+0.054 QALYs) albeit at a slightly higher incremental cost than in the base case (+£5,563 versus +£5,567). The ICER per QALY gained for treatment with Nab-Pac+Gem versus Gem+Cap using revised HRs is £103,827.

The ERG's analysis generates a mean OS loss of 2.72 months and a mean PFS loss of 1.42 months for treatment with Nab-Pac+Gem versus FOLFIRINOX. These results should be treated with caution due to violation of PH in the ACCORD trial.[7] Applying revised HRs in the model results in extra time on treatment for patients receiving FOLFIRINOX, which generates high enough extra administration, monitoring and AE costs to outweigh the more expensive drugs used for treatment with Nab-Pac+Gem. It also increases OS and PFS for treatment with FOLFIRINOX, which in turn increases the incremental QALY difference between Nab-Pac+Gem and FOLFIRINOX. As treatment with Nab-Pac+Gem becomes cheaper than treatment with FOLFIRINOX once the revised HRs are applied (-£582), and remains less beneficial (-0.175 QALYs), it is no longer dominated by FOLFIRINOX. The ICER per QALY gained for treatment with Nab-Pac+Gem versus FOLFIRINOX using revised HRs is £3,327.

Costing of first-line treatments

All first-line drugs included in the company's model are overestimated in the base case. This is principally due to the company not including all available vial/packet sizes in its calculation of costs for first-line treatments, but there is also a small impact from using an average BSA for all patients to estimate average dosage rather than estimating doses based on sex. The ERG has re-estimated weekly drug costs using all vial/packet sizes available to the NHS and using separate BSA values for males and females, as recorded in the CA046 trial (Table 43).

Table 43 First-line treatment costs: company model and ERG estimates

	Nab-Pac+Gem	Gem	Gem+Cap	FOLFIRINOX
Company model	[redacted]	[redacted]	[redacted]	[redacted]
ERG	[redacted]	[redacted]	[redacted]	[redacted]
Difference	[redacted]	[redacted]	[redacted]	[redacted]

Source: BNF; eMIT; MIMs; ERG calculations
Note: these costs do not include amendments for dose intensity or wastage

Applying the ERG's drug costing method decreases the ICER per QALY gained for treatment with Nab-Pac+Gem versus Gem by £7,721 to £39,289. Treatment with Nab-Pac+Gem remains dominated by both treatment with Gem+Cap and treatment with FOLFIRINOX.

Time on treatment

The company uses a stratified Gamma model to estimate time on treatment for patients receiving Nab-Pac+Gem or Gem, which is unnecessary, as the data from the CA046 is complete. The company's stratified Gamma model slightly overestimates time on treatment for both Nab-Pac+Gem and Gem by the same amount (0.23 months), but, given the magnitude of the cost differential between the two treatments, this difference has a sizable impact on the ICER per QALY gained.

Using the full K-M data for time on treatment rather than the company's stratified Gamma model increases the ICER per QALY gained for treatment with Nab-Pac+Gem versus Gem by £2,911 to £49,922. Treatment with Nab-Pac+Gem remains dominated by both treatment with Gem+Cap and treatment with FOLFIRINOX.

5.5.3 Minor issues

AE disutilities

The company base case analysis includes AE disutilities alongside health-state utility values from a clinical trial,[59] which the ERG considers to be double counting. The effects of AEs experienced during a trial will be included in patients' responses to the EQ-5D questionnaire and do not need to be estimated separately. The ERG has used an existing switch in the

company model to remove additional AE disutilities from the calculation of the ICER per QALY gained. Without additional AE disutilities, the ICER per QALY gained for the comparison of treatment with Nab-Pac+Gem versus Gem decreases by £17 to £46,994. Treatment with Nab-Pac+Gem remains dominated by both treatment with Gem+Cap and treatment with FOLFIRINOX.

5.5.4 ERG analyses

Survival estimates: CA046

The company's use of fully parametric models to estimate and extrapolate time-to-event data from the CA046 trial introduces unnecessary uncertainties into the cost effectiveness estimates for the comparison of Nab-Pac+Gem versus Gem. The CA046 trial data are 90% complete for OS and almost 100% complete for PFS, so it is only the very few remaining patients for whom outcomes need to be estimated. By using fully parametric models, the company is replacing with estimates information that already exists for most patients in the CA046 trial. The ERG's preference when modelling survival using data from a single trial is to use K-M data as far as possible before appending a parametric model to the end of the K-M data to project over the remaining time horizon. In NICE TA360,[14] the ERG explored the impact of modelling OS and PFS using only those data in the period towards the end of the survival curve in which it was apparent that a long-term trend had become established (Figure 9 and Figure 10). These estimates are included in the current company model as a sensitivity analysis and are preferred by the ERG in this appraisal.

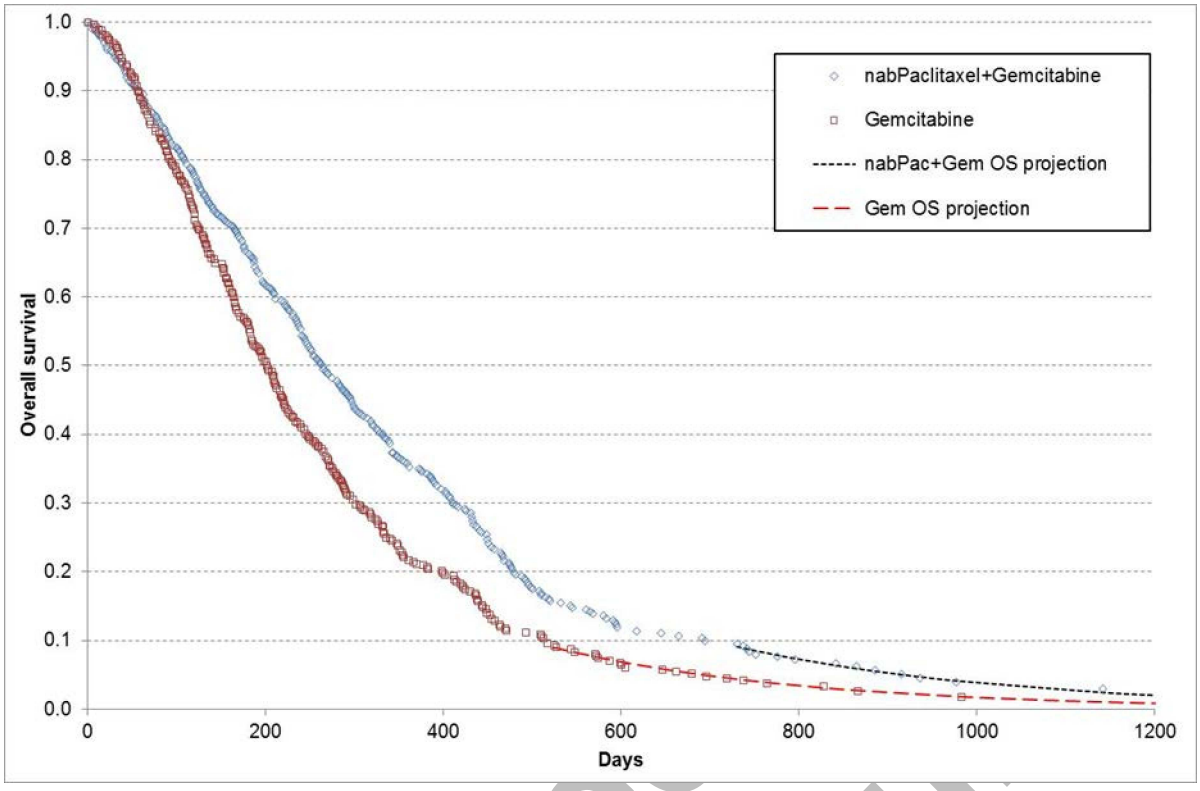

Figure 9 Overall survival in the whole CA046 trial population
Source: NICE TA360

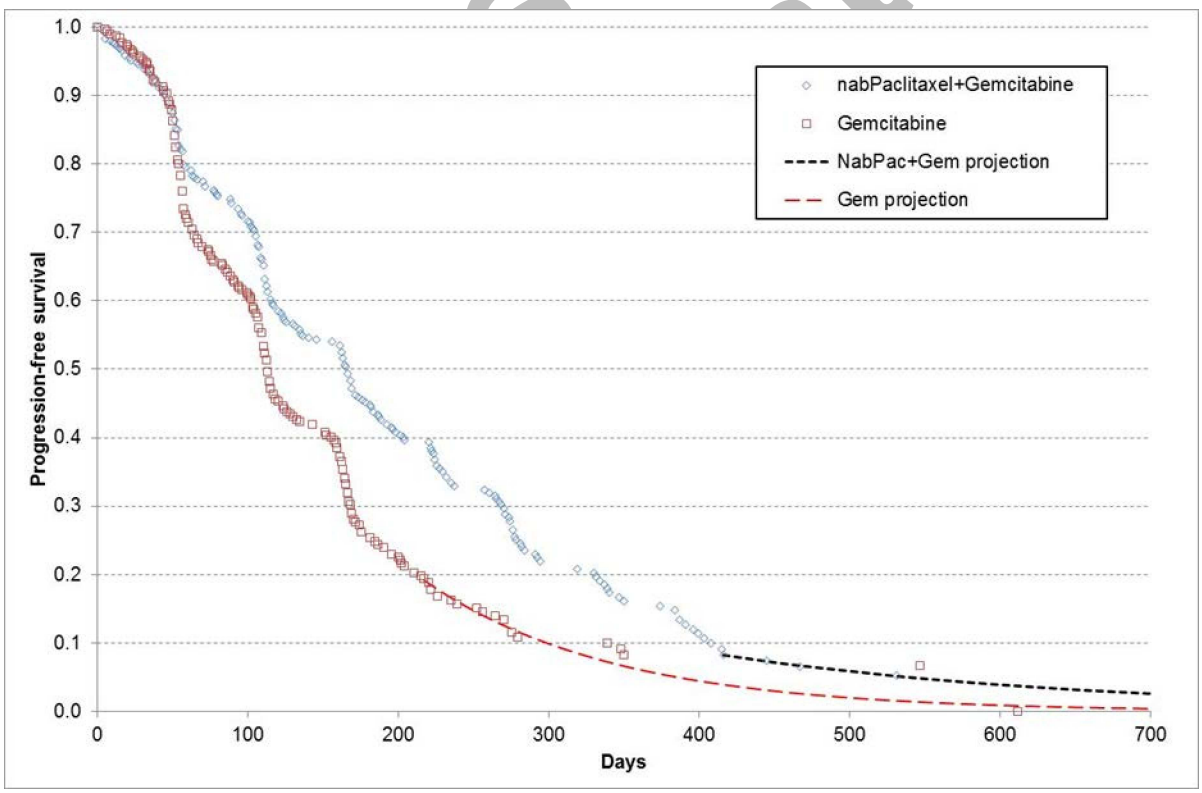

Figure 10 Progression free survival in the whole CA046 trial population
Source: NICE TA360

Using the ERG's OS projections from NICE TA360[14] gives mean OS for treatment with Nab-Pac+Gem of 10.91 months and mean OS for Gem of 8.47 months, resulting in an OS gain of

2.44 months. This is compared to an OS gain of 2.42 months in the company model. Using the ERG estimates of OS, the ICER per QALY gained for treatment with Nab-Pac+Gem versus Gem decreases by £330 to £46,681. Treatment with Nab-Pac+Gem remains dominated by both treatment with Gem+Cap and treatment with FOLFIRINOX.

Using the ERG's PFS projections from NICE TA360[14] gives mean PFS for treatment with Nab-Pac+Gem of 6.82 months and mean PFS for Gem of 4.74 months, resulting in a PFS gain of 2.52 months. This is compared to a PFS gain of 2.07 months in the company model. Using the ERG estimates of PFS, the ICER per QALY gained for treatment with Nab-Pac+Gem versus Gem increases by £77 to £46,933. Treatment with Nab-Pac+Gem remains dominated by both treatment with Gem+Cap and treatment with FOLFIRINOX.

5.5.5 Scenario analyses

AE costs

The ERG has investigated the sensitivity of the ICERs per QALY gained to the estimates of AE costs used in the model. used published sources[68-70] and discussions with a clinical expert to re-estimated the resource cost used in the model for some AEs. The major differences between the ERG estimates of AE costs and the company estimates is in the assumed length of stay in hospital for Grade 3+ diarrhoea, dehydration and vomiting: the ERG has assumed at least one overnight stay for these events, whereas the company has assumed that patients will not stay overnight in hospital. Table 44 gives the definitions of all the admission/appointment types used in the costing of AEs. Table 45 compares the costs used in the company base case versus the ERG revised costs.

Table 44 Definition of admission/appointment types

Type	Definition
Non-elective inpatient short stay	1 day (no overnight - patient allowed home on day of admission)[70]
Non-elective inpatient long stay	2 or more days[70]
Day case	Admitted electively, returns home as scheduled without stay overnight[69]
Outpatient procedure	Attendance at outpatient clinic (pre-booked or not)[70]

Table 45 Costs of Grade 3+ AEs: Company model and ERG revisions

	Company model		ERG	
Grade 3+ AE	**Reference**	**Cost**	**Reference**	**Cost**
Neutropenia	High cost drugs: Neutropenia Drugs, Band 1 (Admitted patient care, HRG code: XD25Z)	£97.29	High cost drugs: Neutropenia Drugs, Band 1 (Outpatient, HRG code: XD25Z)	£136.61
Fatigue	Assumption: Fatigue assumed as one nurse visit per day of fatigue	£35.00	As per CS	£35.00
Thrombocytopenia	Thrombocytopenia with CC Score 0-1 (Non-elective inpatient short stay, HRG code: SA12K)	£498.81	Thrombocytopenia with CC Score 0-1 (Day case, HRG code: SA12K)	£324.52
Anaemia	Iron Deficiency Anaemia with CC Score 0-1 (Non-elective inpatient short stay, HRG code: SA04L)	£481.06	As per CS	£481.06
Leukopenia	No specific data available – assumed to be equal to neutropenia	£97.29	Assume same as neutropenia	£136.61
Peripheral sensory neuropathy (pain)	Pain management (Total outpatient procedures, service code: 191)	£139.12	As per CS	£139.12
Neuropathy peripheral (pain)	Pain management (Total outpatient procedures, service code: 191)	£139.12	As per CS	£139.12
Dehydration	Fluid or Electrolyte Disorders, with Interventions, with CC Score 0-4 (Non-elective inpatient short stay, HRG code: KC05H)	£808.64	Fluid or Electrolyte Disorders, with Interventions, with CC Score 0-4 (Non-elective inpatient long stay, HRG code: KC05H)	£3,368.32
Asthenia	Assumption: Asthenia assumed as one nurse visit per day of asthenia	£35.00	As per CS	£35.00
Abdominal pain	Abdominal Pain with Interventions (Non-elective inpatient short stay, HRG code: FZ90A)	£1,124.81	Abdominal Pain with Interventions (Non elective long stay, HRG code: FZ90A)*	£2,407.05
Nausea	Assumption: same as diarrhoea	£379.38	As per CS	£379.38
Diarrhoea	Non-Malignant Gastrointestinal Tract Disorders without Interventions, with CC Score 0-2, day case [FZ91M]	£379.38	Fluid or Electrolyte Disorders, with Interventions, with CC Score 0-4 (Non-elective inpatient long stay, HRG code: KC05H)	£3,368.32
Vomiting	Assumption: same as diarrhoea	£379.38	Assume same as diarrhoea	£3,368.32
Decreased appetite	Assumption: same as diarrhoea	£379.38	Assume same as nausea	£379.38
Pulmonary embolism	Pulmonary Embolus with Interventions, with CC Score 0-8, non-elective inpatient [DZ09K]	£1,549.87	Pulmonary Embolus with Interventions, with CC Score 0-8 (Non-elective inpatient short stay, HRG code: DZ09K)	£677.69
Pneumonia	Other Respiratory Disorders without Interventions, with CC Score 11+ (Non- elective inpatient long stay, HRG code: DZ19L)	£1,984.07	As per CS	£1,984.07

Febrile Neutropenia	Other Haematological or Splenic Disorders, with CC Score 0-2 (Non-elective inpatient long stay, HRG code: SA08J)	£2,067.07	As per CS	£2,067.07
Cholangitis	Assumption: UK Advisory board estimate 5 x cost of 1 excess bed day from NHS reference manual 2015/2016	£1,530.00	Gastrointestinal Infections without interventions, with CC Score 0-1 (Non-elective inpatient long stay, HRG code: FZ36Q)	£1,421.51
Hyperbilirubinemia	Assumption: UK Advisory board: 1 consultant visit, 5 community nurse visits plus 1 ultrasound	£435.22	Assume same as cholangitis	£1,421.51

* long stay assumed due to need for investigations before deciding on subsequent management
Source: CS Table 68; NHS Reference Costs 2015/2016

Applying all the ERG's revised AE costs increases the ICER per QALY gained for the treatment of Nab-Pac+Gem versus Gem by £1,762 to £48,773. Treatment with Nab-Pac+Gem remains dominated by both treatment with Gem+Cap and treatment with FOLFIRINOX.

Health state utility values

The ERG does not consider any of the utility values presented by the company to be robust. However, it has not identified a preferred source of utility values. The ERG considers the UK-adjusted Romanus[59] and SIEGE crosswalk[58] values to be more appropriate than the SIEGE Devlin[57] values. It has presented the Romanus[59] values in its base case analysis to maintain consistency with previous appraisal TA360[14] in the absence of detail that would allow critique of the values from the SIEGE trial.[28] The SIEGE crosswalk utility values are presented as a sensitivity analysis.

Table 46 Health state utility values

	Health state utility	
	Pre-progression	**Post-progression**
Devlin[57] value set (SIEGE)	0.79	0.75
Crosswalk method[58] (SIEGE)	0.70	0.65
Romanus et al (2012)[59] with UK adjustment	0.74	0.67

Source: CS, Table 52

The company's justification for choosing the Romanus[59] utility values is based on flawed reasoning. The company notes that the two methods of analysing the SIEGE[28] HRQoL data produce substantially different results and that the choice between them is subjective. It also notes that the UK-adjusted Romanus[59] utility values fall between the two sets of values derived from the SIEGE[28] trial, and uses this fact to inform its decision to use the UK-adjusted Romanus[59] values in its base case.

The ERG does not consider it appropriate to categorise the two sets of utility estimates from the SIEGE[28] trial as upper and lower bounds of the health state utility estimates. The Devlin[57] and crosswalk[58] methods are not attempting to produce estimates of the same thing. The Devlin[57] value set is a way of weighting the 3125 theoretically possible health states derived from the EQ-5D-5L questionnaire according to their value by the general UK population. The crosswalk method is a way of translating the results of the EQ-5D-5L into the weighting of the 243 theoretically possible health states derived from the EQ-5D-3L. Out of the three sets of utility values presented by the company, only the UK-adjusted Romanus[59] utility values and the utility values from the SIEGE[28] trial adjusted to the EQ-5D-3L UK-value set are comparable, since they are measured on the same scale.

Since the NICE cost-effectiveness thresholds are based on benefit calculations using HRQoL data derived from the EQ-5D-3L questionnaire, and because the results of the EQ-5D-5L and EQ-5D-3L have been found to produce substantially different estimates of cost effectiveness,[71] the ERG does not consider the Devlin[57] value set to be appropriate in this instance.

The UK-adjusted values from the Romanus paper[59] were the ERG's preferred estimates of health state utility in the original appraisal,[14] at which time the HRQoL data from the SIEGE trial were not available. The ERG noted in the original appraisal that there was still considerable uncertainty around patients' quality of life using these estimates. First, the patients in the trial reported by Romanus[59] were not treated with Nab-Pac+Gem; they received either Gemcitabine plus Placebo or Gemcitabine plus Bevacizumab. Second, the company itself had pointed out that the reported utility values for patients with stable disease in the Romanus[59] study were not significantly different from age-matched US general population values. Third, the utility values were mapped to the UK-value set from published summary values, which introduces further uncertainty.

The SIEGE[28] trial has the greatest relevance to the current appraisal, as it is a UK-based randomised trial that recruited patients with metastatic pancreatic cancer of whom half received the Nab-Pac+Gem regimen used in the CA046 trial. However, the reference provided by the company does not include any details of the EQ-5D from the SIEGE[28] trial, so the ERG has not been able to verify the derivation or mapping of the utility values from the trial.

Applying the switch in the company model to use the SIEGE crosswalk utility values instead of the base case UK-adjusted Romanus utility values increases the ICER per QALY gained for treatment with Nab-Pac+Gem versus Gem by £2,667 to £49,678. Treatment with Nab-

Pac+Gem remains dominated by both treatment with Gem+Cap and treatment with FOLFIRINOX. Applying the switch in the company model to use the SIEGE Devlin[57] utility values instead of the base case UK-adjusted Romanus utility values would decrease the ICER per QALY gained for treatment with Nab-Pac+Gem versus Gem. Treatment with Nab-Pac+Gem would remain dominated by both treatment with Gem+Cap and treatment with FOLFIRINOX.

6 IMPACT ON THE ICER OF ADDITIONAL CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

Before incorporating any ERG amendments into the company model, the ERG has corrected an error in the company model, namely:

- Calculation of total LY and QALYs

The ERG has made the following amendments to the ERG corrected company base case for treatment with Nab-Pac+Gem versus Gem, Nab-Pac+Gem versus Gem+Cap and Nab-Pac versus Gem versus FOLFIRINOX:

- HRs for Gem+Cap vs Gem (R1)
- HRs for FOLFIRINOX vs Gem (R2)
- ERG drug costing method (R3)
- TOT from CA046 trial (R4)
- Do not apply AE disutilities (R5)
- ERG OS (R6)
- ERG PFS (R7)

The ERG has also included two scenario analyses to investigate the effect of changes to the ERG corrected base case of using:

- ERG AE costs (S1)
- SIEGE crosswalk utility values (S2)

Deterministic results

Cost effectiveness results for the base case comparisons of treatment with Nab-Pac+Gem versus Gem, Nab-Pact+Gem versus Gem+Cap and for Nab-Pac+Gem versus FOLFIRINOX are displayed in Table 47, Table 48 and Table 49 respectively. Cost effectiveness results for the sensitivity analyses for comparisons of treatment with Nab-Pac+Gem versus Gem, Nab-Pact+Gem versus Gem+Cap and for Nab-Pac+Gem versus FOLFIRINOX are displayed in Table 50, Table 51 and Table 52 respectively.

When all of the ERG's suggested amendments have been implemented in the base case, the ICER per QALY gained for treatment with Nab-Pac+Gem versus Gem is £41,250. When all of the ERG's suggested amendments have been implemented in the base case and all of the scenario analyses are implemented, the ICER per QALY gained for treatment with Nab-Pac+Gem versus Gem is £45,571.

The ERG urges caution when interpreting its revised cost effectiveness results for treatment with Nab-Pac+Gem versus Gem+Cap and versus FOLFIRINOX, as there are fundamental issues within the time-to-event estimates (non-PH in the ACCORD[7] trial, and the use of HRs with a stratified Gamma model) that it could not resolve within the model.

Treatment with Nab-Pac+Gem is no longer dominated by treatment with Gem+Cap once all of the ERG revisions are applied in combination. This is principally due to the ERG's indirect treatment comparison method (R1), which uses HRs applied to the modelled Gem OS, PFS and TOT to estimate time-to-event outcomes for treatment with Gem+Cap. When all of the ERG's suggested amendments to the base case have been implemented, the ICER per QALY gained for treatment with Nab-Pac+Gem versus Gem+Cap is £99,837. When all of the ERG's suggested amendments have been implemented in the base case and all of the scenario analyses are implemented, the ICER per QALY gained for treatment with Nab-Pac+Gem versus Gem+Cap is £107,898.

Treatment with Nab-Pac+Gem is dominated by treatment with FOLFIRINOX when all but one of the ERG's revisions are applied either individually or in combination. This is because treatment with Nab-Pac+Gem is shown to be more costly and les beneficial than treatment with FOLFIRINOX. The only ERG revision that does not result in treatment with FOLFIRINOX dominating treatment with Nab-Pac+Gem is when the ERG's amended HRs are applied to the model in isolation (R2). This results in extra time on treatment for patients receiving FOLFIRINOX, which generates high enough extra administration, monitoring and AE costs to outweigh the more expensive drugs used for treatment with Nab-Pac+Gem. Treatment with Nab-Pac+Gem thus becomes cheaper than treatment with FOLFIRINOX due to this individual revision and remains less beneficial, and yields an ICER of £3,327. When all of the ERG's suggested amendments have been implemented in the base case and all of the scenario analyses are implemented, treatment with Nab-Pac+Gem is dominated by treatment with FOLFIRINOX.

Table 47 Cost effectiveness results: ERG revisions to company base case for the comparison of Nab-Pac+Gem vs Gem

Description	Nab-Pac+Gem			Gem			Incremental			ICER/QALY gained	ICER change
	Costs	LY	QALYs	Costs	LY	QALYs	Costs	LY	QALYs		
Company original base case	[redacted]	***0.927***	***0.540***	[redacted]	***0.725***	***0.396***	***£6,717***	***0.202***	***0.144***	***£46,657***	**-**
Company updated base case	[redacted]	***0.927***	***0.539***	[redacted]	***0.725***	***0.396***	***£6,755***	***0.202***	***0.144***	***£46,932***	**-**
ERG corrected company base case	[redacted]	***0.908***	***0.527***	[redacted]	***0.706***	***0.383***	***£6,755***	***0.202***	***0.144***	***£47,011***	**-**
R1) HRs for Gem+Cap vs Gem	[redacted]	-	-	[redacted]	-	-	**-**	-	-	**-**	**-**
R2) HRs for FOLFIRINOX vs Gem	[redacted]	0.908	0.527	[redacted]	0.706	0.383	***£6,755***	0.202	0.144	***£47,012***	***+£1****
R3) ERG drug costing method	[redacted]	0.908	0.527	[redacted]	0.706	0.383	***£5,646***	0.202	0.144	***£39,289***	***-£7,721***
R4) TOT from CA046 trial	[redacted]	0.908	0.527	[redacted]	0.706	0.383	***£7,173***	0.202	0.144	***£49,922***	***£2,911***
R5) Do not apply AE disutilities	[redacted]	0.908	0.527†	[redacted]	0.706	0.383†	***£6,755***	0.202	0.144	***£46,994***	***-£17***
R6) ERG OS	[redacted]	0.909	0.528	[redacted]	0.706	0.383†	***£6,750***	0.203	0.145	***£46,681***	***-£330***
R7) ERG PFS	[redacted]	0.908	0.531	[redacted]	0.706	0.387	***£6,765***	0.202	0.144	***£46,933***	***-£77***
ERG revised base case (R3:R7)	[redacted]	***0.909***	***0.532***	[redacted]	***0.706***	***0.387***	***£5,985***	***0.203***	***0.145***	***£41,250***	***-£5,761***

Costs and QALYs discounted; life years undiscounted
* Changing HRs for FOLFIRINOX affects results for other treatments due to calculation of G-CSF use in patients treated with FOLFIRINOX second line
† QALY change from ERG corrected company base case evident at greater than 3 decimal places
AE=adverse event; ERG=Evidence Review Group; LY=life years; PFS=progression free survival; OS=overall survival; QALYs=quality adjusted life years; TOT=time on treatment; ICER=incremental cost effectiveness ratio

Table 48 Cost effectiveness results: ERG revisions to company base case for the comparison of Nab-Pac+Gem vs Gem+Cap

Description	Nab-Pac+Gem			Gem+Cap			Incremental			ICER/QALY gained
	Costs	LY	QALYs	Costs	LY	QALYs	Costs	LY	QALYs	
Company original base case	[redacted]	***0.927***	***0.540***	[redacted]	***0.950***	***0.551***	***£5,555***	***-0.023***	***-0.011***	***Dominated***
Company updated base case	[redacted]	***0.927***	***0.539***	[redacted]	***0.950***	***0.551***	***£5,567***	***-0.023***	***-0.011***	***Dominated***
ERG corrected company base case	[redacted]	***0.908***	***0.527***	[redacted]	***0.931***	***0.538***	***£5,567***	***-0.023***	***-0.011***	***Dominated***
R1) HRs for Gem+Cap vs Gem	[redacted]	0.908	0.527	[redacted]	0.839	***0.473***	***£5,563***	0.068	0.054	***£103,827***
R2) HRs for FOLFIRINOX vs Gem	[redacted]	0.908	0.527	[redacted]	0.931	***0.538***	***£5,568****	-0.023	-0.011	***Dominated***
R3) ERG drug costing method	[redacted]	0.908	0.527	[redacted]	0.931	***0.538***	***£4,520***	-0.023	-0.011	***Dominated***
R4) TOT from CA046 trial	[redacted]	0.908	0.527	[redacted]	0.931	***0.538***	***£5,719***	-0.023	-0.011	***Dominated***
R5) Do not apply AE disutilities	[redacted]	0.908	0.527†	[redacted]	0.931	***0.538†***	***£5,567***	-0.023	-0.011	***Dominated***
R6) ERG OS	[redacted]	0.909	0.528	[redacted]	0.934	***0.539***	***£5,560***	-0.024	-0.012	***Dominated***
R7) ERG PFS	[redacted]	0.908	0.531	[redacted]	0.931	***0.542***	***£5,464***	-0.023	-0.010	***Dominated***
ERG revised base case (R1, R3:R7)	[redacted]	***0.909***	***0.532***	[redacted]	***0.845***	***0.482***	***£5,072***	***0.064***	***0.051***	***£99,837***

Costs and QALYs discounted; life years undiscounted
* Changing HRs for FOLFIRINOX affects results for other treatments due to calculation of G-CSF use in patients treated with FOLFIRINOX second line
† QALY change from ERG corrected company base case evident at greater than 3 decimal places
AE=adverse event; ERG=Evidence Review Group; LY=life years; PFS=progression free survival; OS=overall survival; QALYs=quality adjusted life years; TOT=time on treatment; ICER=incremental cost effectiveness ratio

Table 49 Cost effectiveness results: ERG revisions to company base case for the comparison of Nab-Pac+Gem vs FOLFIRINOX

Description	Nab-Pac+Gem			FOLFIRINOX			Incremental			ICER/QALY gained
	Costs	LY	QALYs	Costs	LY	QALYs	Costs	LY	QALYs	
Company original base case	[redacted]	***0.927***	***0.540***	[redacted]	***1.154***	0.693	£1,542	***-0.227***	***-0.153***	***Dominated***
Company updated base case	[redacted]	***0.927***	***0.539***	[redacted]	***1.154***	0.693	£1,479	***-0.227***	***-0.153***	***Dominated***
ERG corrected company base case	[redacted]	***0.908***	***0.527***	[redacted]	***1.135***	0.680	£1,479	***-0.227***	***-0.153***	***Dominated***
R1) HRs for Gem+Cap vs Gem	[redacted]	-	-	[redacted]	-	-	-	-	-	-
R2) HRs for FOLFIRINOX vs Gem	[redacted]	0.908	0.527	[redacted]	1.170	0.702	-£582	-0.262	-0.175	£3,327
R3) ERG drug costing method	[redacted]	0.908	0.527	[redacted]	1.135	0.680	£592	-0.227	-0.153	Dominated
R4) TOT from CA046 trial	[redacted]	0.908	0.527	[redacted]	1.135	0.680	£2,304	-0.227	-0.153	Dominated
R5) Do not apply AE disutilities	[redacted]	0.908	0.527†	[redacted]	1.135	0.680†	£1,479	-0.227	-0.152	Dominated
R6) ERG OS	[redacted]	0.909	0.528	[redacted]	1.150	0.688	£2,058	-0.225	-0.159	Dominated
R7) ERG PFS	[redacted]	0.908	0.531	[redacted]	1.135	0.686	£16	-0.227	-0.148	Dominated
ERG revised base case (R2:R7)	[redacted]	***0.909***	***0.532***	[redacted]	***1.201***	0.726	£383	***-0.291***	***-0.194***	***Dominated***

Costs and QALYs discounted; life years undiscounted

† QALY change from ERG corrected company base case evident at greater than 3 decimal places

AE=adverse event; ERG=Evidence Review Group; LY=life years; PFS=progression free survival; OS=overall survival; QALYs=quality adjusted life years; TOT=time on treatment; ICER=incremental cost effectiveness ratio

Table 50 Cost effectiveness results: ERG base case sensitivity analysis for the comparison of Nab-Pac+Gem vs Gem

Description	Nab-Pac+Gem			Gem			Incremental			ICER/QALY gained	ICER change
	Costs	LY	QALYs	Costs	LY	QALYs	Costs	LY	QALYs		
Company original base case	[redacted]	***0.927***	***0.540***	[redacted]	***0.725***	***0.396***	***£6,717***	***0.202***	***0.144***	***£46,657***	**-**
Company updated base case	[redacted]	***0.927***	***0.539***	[redacted]	***0.725***	***0.396***	***£6,755***	***0.202***	***0.144***	***£46,932***	**-**
ERG corrected company base case	[redacted]	***0.908***	***0.527***	[redacted]	***0.706***	***0.383***	***£6,755***	***0.202***	***0.144***	***£47,011***	**-**
ERG revised base case (R3:R7)	[redacted]	***0.909***	***0.532***	[redacted]	***0.706***	***0.387***	***£5,985***	***0.203***	***0.145***	***£41,250***	***-£5,761***
S1) ERG AE costs	[redacted]	0.908	0.527	[redacted]	0.706	0.383	***£7,008***	0.202	0.144	***£48,773***	***+£1,762***
S2) SIEGE crosswalk utility values	[redacted]	0.908	0.496	[redacted]	0.706	0.360	***£6,755***	0.202	0.136	***£49,678***	***+£2,667***
ERG revised base case + ERG AE costs (S1)	[redacted]	***0.909***	***0.532***	[redacted]	***0.706***	***0.387***	***£6,252***	***0.203***	***0.145***	***£43,088***	***-£3,923***
ERG revised base case + SIEGE crosswalk utilities (S2)	[redacted]	***0.909***	***0.500***	[redacted]	***0.706***	***0.363***	***£5,985***	***0.203***	***0.137***	***£43,626***	***-£3.385***
ERG revised base case + SIEGE crosswalk utilities + ERG AE costs (S1:S2)	[redacted]	***0.909***	***0.500***	[redacted]	***0.706***	***0.363***	***£6,252***	***0.203***	***0.137***	***£45,571***	***-£1,440***

Costs and QALYs discounted; life years undiscounted
AE=adverse event; ERG=Evidence Review Group; LY=life years; QALYs=quality adjusted life years; ICER=incremental cost effectiveness ratio

Table 51 Cost effectiveness results: ERG base case sensitivity analysis for the comparison of Nab-Pac+Gem vs Gem+Cap

Description	Nab-Pac+Gem			Gem+Cap			Incremental			ICER/QALY gained
	Costs	LY	QALYs	Costs	LY	QALYs	Costs	LY	QALYs	
Company original base case	[redacted]	***0.927***	***0.540***	[redacted]	***0.950***	***0.551***	***£5,555***	***-0.023***	***-0.011***	***Dominated***
Company updated base case	[redacted]	***0.927***	***0.539***	[redacted]	***0.950***	***0.551***	***£5,567***	***-0.023***	***-0.011***	***Dominated***
ERG corrected company base case	[redacted]	***0.908***	***0.527***	[redacted]	***0.931***	***0.538***	***£5,567***	***-0.023***	***-0.011***	***Dominated***
ERG revised base case (R1, R3:R7)	[redacted]	***0.909***	***0.532***	[redacted]	***0.845***	***0.482***	***£5,072***	***0.064***	***0.051***	***£99,837***
S1) ERG AE costs	[redacted]	0.908	0.527	[redacted]	0.931	0.538	***£5,600***	***-0.023***	***-0.011***	***Dominated***
S2) SIEGE crosswalk utility values	[redacted]	0.908	0.496	[redacted]	0.931	0.508	***£5,567***	***-0.023***	***-0.012***	***Dominated***
ERG revised base case + ERG AE costs (S1)	[redacted]	***0.909***	***0.532***	[redacted]	***0.845***	***0.482***	***£5,133***	***0.064***	***0.051***	***£101,037***
ERG revised base case + SIEGE crosswalk utilities (S2)	[redacted]	***0.909***	***0.500***	[redacted]	***0.845***	***0.453***	***£5,072***	***0.064***	***0.048***	***£106,616***
ERG revised base case + SIEGE crosswalk utilities + ERG AE costs (S1:S2)	[redacted]	***0.909***	***0.500***	[redacted]	***0.845***	***0.453***	***£5,133***	***0.064***	***0.048***	***£107,898***

Costs and QALYs discounted; life years undiscounted
AE=adverse event; ERG=Evidence Review Group; LY=life years; QALYs=quality adjusted life years; ICER=incremental cost effectiveness ratio

Table 52 Cost effectiveness results: ERG base case sensitivity analysis for the comparison of Nab-Pac+Gem vs FOLFIRINOX

Description	Nab-Pac+Gem			FOLFIRINOX			Incremental			ICER/QALY gained
	Costs	LY	QALYs	Costs	LY	QALYs	Costs	LY	QALYs	
Company original base case	[redacted]	***0.927***	***0.540***	[redacted]	***1.154***	***0.693***	***£1,542***	***-0.227***	***-0.153***	***Dominated***
Company updated base case	[redacted]	***0.927***	***0.539***	[redacted]	***1.154***	***0.693***	***£1,479***	***-0.227***	***-0.153***	***Dominated***
ERG corrected company base case	[redacted]	***0.908***	***0.527***	[redacted]	***1.135***	***0.680***	***£1,479***	***-0.227***	***-0.153***	***Dominated***
ERG revised base case (R2:R7)	[redacted]	***0.909***	***0.532***	[redacted]	***1.201***	***0.726***	***£383***	***-0.291***	***-0.194***	***Dominated***
S1) ERG AE costs	[redacted]	0.908	0.527	[redacted]	1.135	0.680	***£1,559***	***-0.227***	-0.153	Dominated
S2) SIEGE crosswalk utility values	[redacted]	0.908	0.496	[redacted]	1.135	0.641	***£1,479***	***-0.227***	-0.145	Dominated
ERG revised base case + ERG AE costs (S1)	[redacted]	***0.909***	***0.532***	[redacted]	***1.201***	***0.726***	***£436***	***-0.291***	***-0.194***	***Dominated***
ERG revised base case + SIEGE crosswalk utilities (S2)	[redacted]	***0.909***	***0.500***	[redacted]	***1.201***	***0.684***	***£383***	***-0.291***	***-0.184***	***Dominated***
ERG revised base case + SIEGE crosswalk utilities + ERG AE costs (S1:S2)	[redacted]	***0.909***	***0.500***	[redacted]	***1.201***	***0.684***	***£435***	***-0.291***	***-0.184***	***Dominated***

Costs and QALYs discounted; life years undiscounted
AE=adverse event; ERG=Evidence Review Group; LY=life years; QALYs=quality adjusted life years; ICER=incremental cost effectiveness ratio

6.1 Conclusions of the cost effectiveness section

The various changes implemented by the ERG for the comparison of treatment with Nab-Pac+Gem versus Gem, treatment with Nab-Pac+Gem versus Gem+Cap and treatment with Nab-Pac+Gem versus FOLFIRINOX yield a mixture of effects. Incremental costs and incremental benefits both increase and decrease depending on the individual revision. However, none of the ERG's individual revisions or revised base case scenarios yield ICERs under £30,000 per QALY gained for treatment with Nab-Pac+Gem against any of the comparators. Only the comparison of Nab-Pac+Gem versus Gem yields ICERs under £50,000 per QALY gained once all the ERG's revisions and scenarios are applied.

7 END OF LIFE

The NICE End of Life criteria, and the data presented by the company to show that these criteria have been met, are presented in Table 53.

Table 53 End of Life criteria

NICE End of Life criteria	Data presented by the company
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	Real world survival Median: 2 to 6 months depending on how much the cancer has grown and where it has spread Trial survival Median: 6.6 months Mean: 8.7 months Data source: CRUK (real world survival); CA046 extension trial data (trial survival)
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	Survival extension Median: 2.1 months Mean: 2.4 months Data source: CA046 extension trial data (trial survival)

Source: CS, Table 30

7.1 Short life expectancy

The ERG agrees with the company that patients with pancreatic metastatic adenocarcinoma have a life expectancy of less than 24 months.

7.2 Extension to life

An examination of the ERG's remodelled OS suggests that treatment with Nab-Pac+Gem generates a mean survival gain of 2.44 months when compared to gemcitabine.

When treatment with Nab-Pac+Gem is compared with Gem+Cap or FOLFIRINOX, the results from the company base-case NMA show that there is no statistically significant OS gain from Nab-Pac+Gem. The ERG is not aware of any other evidence to support or refute this claim.

8 OVERALL CONCLUSIONS

The ERG considers that the evidence submitted by the company largely reflects the decision problem defined in the final scope issued by NICE. However, direct clinical effectiveness evidence was only available for the comparison of the efficacy of Nab-Pac+Gem versus Gem.

8.1 Direct clinical evidence

The direct clinical effectiveness evidence for the treatment of Nab-Pac+Gem versus Gem was derived from the CA046 trial. This trial, which is complete, was of good quality and no patient crossover was permitted. These attributes mean that it is possible to draw reasonable conclusions from the data about the comparative efficacy of the two interventions in the trial population. Results from the most recent OS analysis (updated analysis) of the CA046 trial data suggest that treatment with Nab-Pac+Gem statistically significantly improves median OS in comparison to treatment with Gem (8.7 months versus 6.6 months; HR=0.72, 95% CI: 0.62 to 0.83). The ERG highlights that the company's OS HR should be viewed with caution as the method used to calculate the OS HR relies on an assumption of PH, which does not hold. The company states that updated OS analysis results[37] show mean OS to be 11.1 months in the Nab-Pac+Gem arm and 8.7 months in the Gem arm.

However, the ERG notes that only 10% of the trial population were aged ≥75 years. Figures from CRUK[16] indicate that, in the NHS, 47% of patients with pancreatic cancer are ≥75 years, and 80% of patients diagnosed with pancreatic cancer have late stage disease. This is of concern as the EMA cautions[9] that there is no demonstrated benefit of treatment with Nab-Pac+Gem in people aged ≥75 years and that patients aged ≥75 years who were treated with Nab-Pac+Gem in the CA046 trial experienced more AEs and SAEs than the overall trial population.

The ERG considers that the company has failed to clearly define the patient population for whom treatment with Nab-Pac+Gem is appropriate. Figures from the company's own market research, based on patient chart audit of first-line therapies, suggest [redacted] of patients received gemcitabine monotherapy, [redacted] received gemcitabine doublet therapy (other than Nab-Pac+Gem) and [redacted] received FOLFIRINOX. The company is confident that all patients who can tolerate FOLFIRINOX can be easily identified in clinical practice; however, the characteristics of these patients have not been described in the CS. The company says that all patients who are fit enough to be treated with FOLFIRINOX are fit enough to be treated with Nab-Pac+Gem. However, the company considers that not all patients who are fit enough to tolerate treatment with Nab-Pac+Gem will be able to tolerate

treatment with FOLFIRINOX. The company considers that Gem is the only relevant comparator but the ERG has not found their case to be compelling.

8.2 Indirect evidence

The company has provided indirect clinical evidence to allow the comparative efficacy of Nab-Pac+Gem versus Gem+Cap and versus FOLFIRINOX to be assessed.

Despite the fact that a connected network could be formed by including only trials that compared treatments relevant to the decision problem, the company base-case network included seven trials[41-47] that provided evidence for treatments that were not listed in the final scope issued by NICE. However, the company performed a sensitivity analysis using a reduced network (fixed effects) that included only the comparators listed in the final scope issued by NICE and the ERG considers the results from this analysis are more valid than the company's base-case NMA results. In terms of OS, the results from this sensitivity analysis mirror the results from the base-case analysis and do not suggest a statistically significant treatment effect for Nab-Pac+Gem versus Gem+Cap (HR=1.10, 95% CrI: 0.67 to 1.84) or for Nab-Pac+Gem versus FOLFIRINOX (HR=0.77, 95% CrI: 0.58 to 1.01). The results from the company's base-case NMA are used in the company's cost effectiveness model.

However, the ERG highlights that all of the NMA OS results are affected by the lack of PH in the CA046 and ACCORD trials[7] and should be interpreted with caution. Furthermore, PFS results are affected by the lack of PH in the CA046 trial and these results should, therefore, also be interpreted with caution.

8.3 Economic evidence

Uncertainty in the modelling of time-to-event outcomes for treatment with Nab-Pac+Gem versus Gem is not limited by the maturity of the CA046 trial, as the trial data are almost complete. However, the company has introduced unnecessary uncertainty back into the model by using parametric models to estimate TOT data that were already complete.

The ERG considers the company's modelling of treatment with Nab-Pac+Gem versus Gem+Cap and versus FOLFIRINOX to be flawed. The modelling relies on HRs from the NMA, which should be treated with caution due to violation of the PH assumption in the CA046 trial. The ERG notes that applying HRs directly from the relevant trials [6,7] to modelled time-to-event estimates for treatment with Gem produces results that do not rely on the PH assumption holding in the CA046 trial. However, the PH assumption does not appear to hold for time-to-event outcomes in the ACCORD[7] trial, so results for FOLFIRINOX should be treated with caution. Although the PH assumption appears to hold in the Scheithauer trial,[6]

the sample is small and data have been digitised, so the ERG's modelling will still be subject to some uncertainty.

There is an absence of HRQoL evidence from the CA046 trial, which introduces further uncertainty into the model. Utility values used in the company's base case and scenario analyses are either from published sources referencing populations treated in different geographies with different interventions,[59] or from unpublished EQ-5D-5L (rather than 3L) data to which the ERG has not had access.[28]

The company has estimated the cost of each treatment in the model based on only a selection of the vial sizes available for each drug. This means that full economies of scale cannot be taken into account in its calculations and that weekly treatment costs are overestimated in its model.

8.4 Implications for research

The ERG considers that further research is required to address several issues. First, there is no direct evidence that can be used to assess the clinical effectiveness of treatment with Nab-Pac+Gem versus Gem+Cap or versus FOLFIRINOX. Second, most of the patients recruited to the CA046 trial are younger than the patients likely to be treated in the NHS, as only 10% of patients of trial patients were aged ≥75 years. Third, the company claims that there are easily identifiable subgroups of patients with metastatic adenocarcinoma pancreatic cancer. However, the characteristics of these patients have not been described in the CS.

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10 APPENDICES

10.1 Key points from the Final Appraisal Determination

TA360 Paclitaxel as albumin-bound nanoparticles in combination with gemcitabine for previously untreated metastatic pancreatic cancer		Section
Key conclusion		
Paclitaxel as albumin-bound nanoparticles in combination with gemcitabine is not recommended within its marketing authorisation for adults with previously untreated metastatic adenocarcinoma of the pancreas. Nab-paclitaxel plus gemcitabine was more clinically effective compared with gemcitabine alone, but was associated with a higher rate of grade 3 or higher adverse effects. FOLFIRINOX was likely to be more clinically effective than nab-paclitaxel plus gemcitabine. Nab-paclitaxel plus gemcitabine and gemcitabine plus capecitabine showed similar progression-free survival and overall survival, but nab-paclitaxel plus gemcitabine may be associated with a higher rate of grade 3 or 4 adverse events. The Committee agreed that the most plausible ICER, allowing for the uncertainty of time-to-event modelling, would lie somewhere between £72,500 and the £78,500 per QALY gained. The company's analyses showed that nab-paclitaxel plus gemcitabine was dominated by FOLFIRINOX and had an ICER of £87,100 per QALY gained compared with gemcitabine plus capecitabine. Although these estimates were subject to considerable uncertainty, the Committee was confident that nab-paclitaxel plus gemcitabine would not be considered a cost effective use of NHS resources compared with these treatments.		1.1, 4.5, 4.7, 4.8, 4.16, 4.17
Current practice		
Clinical need of patients, including the availability of alternative treatments	Previously untreated metastatic pancreatic cancer is associated with a poor prognosis: many people are not diagnosed until the cancer is very advanced and, without treatment, survival may be only 2 to 6 months. Current treatments are limited in efficacy or associated with significant toxicity. Therefore there is value of additional treatment options in this area.	4.2
The technology		
Proposed benefits of the technology How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	The Committee understood that nab-paclitaxel is a novel formulation of paclitaxel and that there was a high level of unmet need in this disease area. However, the Committee considered that all health-related benefits had been adequately captured by the quality-adjusted life years (QALYs) in the model, and it agreed that nab-paclitaxel did not offer a step change in the treatment of metastatic pancreatic cancer.	4.21
What is the position of the treatment in the pathway of care for the condition?	The Committee agreed that nab-paclitaxel plus gemcitabine would be considered for use in clinical practice for those people who were able to tolerate the associated adverse events.	4.3
Adverse reactions	The Committee heard from the clinical expert that the adverse effects of nab-paclitaxel plus gemcitabine, though serious, were mainly manageable. The Committee noted, on reviewing the adverse event profiles from study CA046 and the Conroy study, that both nab- paclitaxel plus gemcitabine and FOLFIRINOX were associated with considerable toxicity, and that a difference in the adverse event profiles could not be reliably determined from the data available.	2.3, 4.2, 4.7

	The most common clinically significant adverse reactions for nab-paclitaxel are: neutropenia, peripheral neuropathy, arthralgia/myalgia and gastrointestinal disorders.	
Evidence for clinical effectiveness		
Availability, nature and quality of evidence	The company's submission presented clinical effectiveness evidence from study CA046. Study CA046 was a phase III international, multicentre, open-label, randomised study comparing nab-paclitaxel plus gemcitabine with gemcitabine alone in people with metastatic pancreatic adenocarcinoma who had not been treated for metastatic disease before, and who had a Karnofsky performance status of 70 or more.	3.2
Relevance to general clinical practice in the NHS	Compared with people treated in clinical practice in England, people in study CA046 were younger and fitter. In addition, there were no participating treatment centres for study CA046 in the UK.	3.24
Uncertainties generated by the evidence	No head-to-head trial data were available comparing nab-paclitaxel plus gemcitabine with FOLFIRINOX or with gemcitabine plus capecitabine. No health-related quality of life data were collected in study CA046, and as such the Committee considered it difficult to judge people's preferences and the acceptability of the toxicity profile of nab-paclitaxel plus gemcitabine.	4.6, 4.5
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	The company's submission presented an analysis for a subgroup of people with a Karnofsky performance status of 70 or 80. The Committee concluded that, based on the biological and clinical plausibility, and the strength of evidence of a subgroup effect, it could not justify excluding people with a Karnofsky performance status of 90 or 100 from its consideration, and therefore it was not appropriate to make recommendations for nab- paclitaxel plus gemcitabine in the subgroup of people with a Karnofsky performance status or 70 or 80. The Committee agreed that it was appropriate to consider the intention-to-treat analyses.	4.9
Estimate of the size of the clinical effectiveness including strength of supporting evidence	Study CA046 showed that nab-paclitaxel plus gemcitabine compared with gemcitabine alone had statistically significantly longer overall survival (median gain of 2.1 months) and progression-free survival (median gain of 1.8 months), and higher response rates (relative risk of 3.19 to 3.81). The mixed treatment comparison showed that nab-paclitaxel plus gemcitabine was likely to be associated with a shorter overall survival and progression-free survival compared with FOLFIRINOX, and with a similar overall survival and progression-free survival compared with gemcitabine plus capecitabine.	3.3, 4.7, 4.8
Evidence for cost effectiveness		
Availability and nature of evidence	The company submitted a de novo economic model to estimate the cost effectiveness of nab-paclitaxel plus gemcitabine with gemcitabine alone in people with metastatic pancreatic cancer that had not been treated	3.12, 3.14

	before. The company also presented scenario analyses comparing nab-paclitaxel plus gemcitabine with FOLFIRINOX and with gemcitabine plus capecitabine. The company used indirect methods to estimate overall survival, progression-free survival and time-on-treatment curves for these comparators which were then used in the model.	
Uncertainties around and plausibility of assumptions and inputs in the economic model	The company made assumptions relating to the costs, utilities and survival estimates in the model. The Committee agreed it was not appropriate to account for vial sharing or missed and reduced doses in the base case. The Committee agreed that the UK EQ-5D algorithm should be used to determine utility values, rather than that of the USA as provided by the company. The company's and ERG's methods of modelling time-to-event data were both associated with strengths and limitations and therefore the Committee considered them equally appropriate.	4.11 to 4.15
Incorporation of health- related quality-of-life benefits and utility values Have any potential significant and substantial health- related benefits been identified that were not included in the economic model, and how have they been considered?	The utility values provided by the Company used a US EQ-5D algorithm. The Committee agreed that the ERG's adjusted utility values, which used the UK algorithm, were the most appropriate. The Committee considered that all health-related benefits had been adequately captured by the quality-adjusted life years (QALYs) in the model.	4.14, 4.21
Are there specific groups of people for whom the technology is particularly cost effective?	The Committee concluded that it was not appropriate to consider nab-paclitaxel plus gemcitabine for a subgroup defined only by performance status.	4.9
What are the key drivers of cost effectiveness?	Deterministic sensitivity analyses showed that the key driver of the cost effectiveness of nab-paclitaxel plus gemcitabine compared with gemcitabine alone was overall survival benefit.	3.20
Most likely cost- effectiveness estimate (given as an ICER)	The Committee agreed that the most plausible ICER for nab-paclitaxel plus gemcitabine compared with gemcitabine alone, allowing for the uncertainty of time-to-event modelling, would lie somewhere between £72,500 and £78,500 per QALY gained. The company's analyses showed that nab-paclitaxel plus gemcitabine was dominated by FOLFIRINOX and had an ICER of £87,100 per QALY gained compared with gemcitabine plus capecitabine. These analyses were estimated from the mixed treatment comparison using the results from the advanced pancreatic cancer population. If the results from the metastatic pancreatic cancer population were used, nab-paclitaxel plus gemcitabine may be dominated by gemcitabine plus capecitabine.	4.16, 4.17
Additional factors taken into account		
Patient access schemes (PPRS)	Not applicable to this appraisal.	
End-of-life considerations	Nab-paclitaxel plus gemcitabine did not meet the extension-to-life criterion when compared with FOLFIRINOX or gemcitabine plus capecitabine. For the comparison of nab-paclitaxel plus gemcitabine with	4.19, 4.20

	gemcitabine alone, the Committee accepted that the end-of-life criteria could be applied when taking into consideration both the relative magnitude of the overall survival gain, and the impact of giving proportionally greater weight to QALYs gained in this condition. The Committee agreed that this was an unusual circumstance and that applying the maximum weighting would not be appropriate. In addition, it noted that this would apply only to those people for whom FOLFIRINOX and gemcitabine plus capecitabine are not suitable treatment options.	
Equalities considerations and social value judgements	No issues relating to equality considerations were raised in the submissions, during consultation or in the Committee meetings.	

Source: NICE Final Appraisal Determination document[25]

Appeal by the company

The company lodged an appeal against the FAD issued by NICE. The appeal was based on the grounds set out in Box 6.

Box 6 Company's appeal grounds

- 1.1(a) The Institute had acted unfairly in failing to consider the impact of the 2014 Pharmaceutical Price Regulation Scheme (PPRS) in determining the cost effectiveness of the technology
- 1.2 (a) The Institute had acted unfairly in failing to obtain sufficient clinical expert input at the second Appraisal Committee meeting
- 2. The Institute had formulated guidance which cannot be reasonably justified in the light of the evidence submitted
- 2.1 That the Appraisal Committee had acted unreasonably in failing to accept a subgroup defined according to performance status, which was proposed by the company with an approvable level of cost effectiveness but not accepted by NICE
- 2.2 That the Appraisal Committee had acted unreasonably in failing to consider adequately the effect of dose adjustments and vial sharing on the calculation of ICERs
- 2.3 That the Appraisal Committee had acted unreasonably in failing to apply the appropriate level of weighting under the end-of-life policy to the QALY, given the extent of survival improvement conferred by Nab-Pac
- 2.4 That the Appraisal Committee had acted unreasonably in deciding that Nab-Pac does not represent a step change in the management of pancreatic cancer

Source: NICE appeal decision[14]

The findings of the Appeal Panel are set out in Box 7.

Box 7 Findings of the Appeal Panel

The Appeal Panel upheld the appeal on the grounds that The Institute had acted unfairly in failing to consider the impact of the 2014 Pharmaceutical Price Regulation Scheme (PPRS) in determining the cost effectiveness of the technology; and that the Appraisal Committee may have acted unreasonably in failing to apply the appropriate level of weighting under the end-of-life policy to the quality-adjusted life year (QALY), given the extent of survival improvement conferred by nab-paclitaxel in so far as it had failed to give clear reasons why it had failed to apply the full weighting.

The appeal was dismissed on all other grounds.

Source: NICE appeal decision[14]

10.2 Comparison of AEs of Grade 3 and above reported in the Conroy and the CA046 trials

Comparison of AEs of Grade 3 and above reported (by 5% patients) in the Conroy and the CA046 trials

Event	FOLFIRINOX (Conroy) N=171	Nab-Pac+Gem N=421
Neutropenia	45.7%	33%
Febrile Neutropenia	5.4%	NR
Thrombocytopenia	9.1%	13%
Anaemia	7.8%	12%
Fatigue	23.6%	18%
Vomiting	14.5%	6%
Diarrhoea	12.7%	6%
Peripheral neuropathy	9.0%	17%
Elevated alanine aminotransferase	7.3%	NR
Thromboembolism	6.6%	5%

NR=not reported
Source: Conroy 2011, CS, Table 22

10.3 Additional safety data

The company reports safety data from the SIEGE trial,[28] a UK multicentre randomised phase II trial comparing different schedules of nab-Paclitaxel combined with Gem as a first-line treatment for metastatic pancreatic cancer (CS, p114). In the SIEGE trial, patients were randomised either to the sequential arm (n=71) where Gem was administered 24 hours after Nab-Pac, or to the concomitant arm (n=75) where Gem was administered immediately after Nab-Pac. The median age of the participants in the SIEGE trial was 67 years (range: 48 to 82). Similar rates to the CA046 trial of Grade ≥3 AEs were observed (n=61, 82%) with the most common (≥10%) being neutropenia (30%), fatigue (15%), febrile neutropenia (12%), and vomiting (11%) (Table 54). A higher rate of myelosuppression across the study was noted; the authors of the publication suggested that this reflected the lower use of growth factor support (G-CSF received by 12 patients in the concomitant arm [16%]) compared to that received in the CA046 trial.

The CS also included safety data from retrospective studies (CS, pp114-121). There were some differences when compared to the CA046 trial. A study conducted in the UK (n=32) observed rates of Grade 3 peripheral neuropathy of 3.1% with no patients developing Grade 3 or 4 toxicities of neutropenia.[40] In an Italian setting, 13 out of 208 patients experienced a Grade 4 TEAE; with the most common being Grade 4 neutropenia observed in 4% of patients (n=8).[23] Subgroup analysis of the Italian cohort compared patients <75 years (n=176) to those ≥75 years of age (n=32) and the company suggested that the toxicity profile of Nab-Pac+Gem was similar across the patient groups (CS, p117).

Table 54 Adverse events (Grade ≥3) in the CA046 trial, SIEGE trial and from an Italian setting

Category of event	Nab-Pac+Gem N=421 n (%)	SIEGE concomitant arm N=74 n (%)	Italian setting N=208 n (%)
At least one Grade ≥3 AE	374 (89)	61 (82)	-
Neutropenia	138 (33)	22 (30)	50 (24)
Thrombocytopenia	53 (13)	7 (10)	31 (15)
Anaemia	49 (12)	4 (5)	5 (2)
Leukopenia	39 (9)	3 (4)	-
Fatigue	77 (18)	11 (15)	35 (17)
Diarrhoea	26 (6)	3 (4)	11 (5)
Nausea	27 (6)	2 (3)	-
Vomiting	25 (6)	8 (11)	-
Nausea / vomiting	-	-	9 (4)
Dehydration	31 (7)	3 (4)	-

AE=adverse event
Source: CS, p114, Table 22, Table 26

10.4 ERG summary of characteristics of studies included in the base case network of evidence

The company highlights that patient demographics were generally well balanced between the trials included in the NMA, although there were differences in the ethnicity of included patients (CS, p80). For example, two trials[44,47] included exclusively Asian populations. Differences in clinical characteristics were observed between the trials in terms of the extent of metastatic disease (number of metastatic sites and location of metastases), CA19-9 levels, and tumour location which can be associated with presence of a biliary stent. Furthermore, the company explains that it is difficult to make comparisons of performance status (PS) between patients in the included trials due to differences in the assessment criteria used by the trial investigators. There are also differences in the measurement of disease progression between patients in the included trials; some investigators used RECIST criteria (also used in the CA046 trial), while others used alternative criteria such as those developed by the World Health Organization (WHO). It also remains unknown whether disease progression was investigator- or independently-assessed in most of the included trials, and some trial investigators collected time to progression (TTP) data rather than PFS data.

10.5 Trial methodology of studies in the reduced network of evidence

Table 55 Summary of trial methodology for studies in the reduced network of evidence

	ACCORD[7]	Scheithauer 2003[6]	CA046[12]
Location	55 study locations in France	Austria	151 sites in North America, Australia, Russia, Italy, Canada, Ukraine, Spain, Germany, Austria, France and Belgium.
Trial design	A multicentre, randomised, Phase II-III trials to explore FOLFIRINOX compared with single-agent Gem as first-line treatment in patients with metastatic cancer	A multicentre, randomised Phase II trial to investigate the feasibility and therapeutic index of a bi-weekly high-dose Gem+Cap versus Gem alone in previously untreated patients with advanced metastatic adenocarcinoma	Phase III, international, multi-centre, open-label RCT. Randomisation was stratified by key prognostic factors: geographic region (North America vs other), baseline KPS (70–80 vs 90–100), and presence of liver metastases (yes vs no)
Eligibility criteria for participants	≥18 years of age; histologically and cytologically confirmed, measurable metastatic pancreatic adenocarcinoma that had not previously been treated with chemotherapy; ECOG PS of 0–1; adequate bone marrow (granulocyte count ≥1500/mm^3 and platelet count ≥100,000/mm^3), liver function (bilirubin ≤1.5 times the upper limit of the normal range, and renal function. Patients were excluded if they were aged 76 years of older; endocrine or acinar pancreatic carcinoma; previous radiotherapy for measurable lesions; cerebral metastases; history of another major cancer; active infection;	Histologically or cytologically ascertained metastatic adenocarcinoma of the exocrine pancreas; bidimensionally measurable disease; age between 19 and 75 years; an anticipated life expectancy of ≥3 months; a baseline KPS of ≥50%; adequate renal (serum creatinine level <1.5mg/dL), liver (total bilirubin level <1.5mg/dL and transaminase levels <2 X ULN) and bone marrow function (leucocyte count ≥4000/µl, absolute neutrophil count ≥2,000/µl and platelet count ≥100,000/µl); patients may have received adjuvant fluoropyrimidine-based chemotherapy and/or radiation therapy, but this must have been completed at least 6 months before study entry; a minimum of 2 weeks was required to have elapsed in cases of prior abdominal exploration or palliative surgery. Patients were excluded if they had resectable tumours; locally advanced inoperable disease; other serious or uncontrolled concurrent medical illness; central nervous system metastases; any prior palliative chemotherapy	Eligible adults (≥18 years of age) had a KPS score of 70 or more (on a scale from 0 to 100, with higher scores indicating better performance status), had not previously received chemotherapy for metastatic disease, and had histologically or cytologically confirmed metastatic adenocarcinoma of the pancreas that was measurable according to RECIST version 1.0. Metastatic disease had to have been diagnosed within 6 weeks before randomization. Eligible patients could have received treatment with fluorouracil or Gem as a radiation sensitizer in the adjuvant setting if the treatment had been received at least 6 months before randomization. Patients who had received cytotoxic doses of Gem or any other chemotherapy in the adjuvant setting and those with islet-cell neoplasms or locally advanced disease were excluded. Patients had to have adequate hematologic, hepatic, and renal function (including an absolute neutrophil count of ≥1.5×10 per liter, a hemoglobin level of ≥9 g per deciliter, and a bilirubin level at or below the ULN range, according to the standards at the central laboratory)

<table>
<tr><th></th><th>ACCORD[7]</th><th>Scheithauer 2003[6]</th><th>CA046[12]</th></tr>
<tr><td></td><td>chronic diarrhoea; clinically significant history of cardiac disease; pregnancy or breast-feeding</td><td></td><td></td></tr>
<tr><td>Trial drugs</td><td>FOLFIRINOX: oxaliplatin 85mg/m^2 by 2-hour IV infusion, immediately followed by leucovorin 400mg/m^2 by 2-hour IV infusion, with the addition after 30 minutes of irinotecan 180mg/m^2 by 90-minute IV infusion, followed immediately by fluorouracil 400mg/m^2 by IV bolus, followed by a continuous IV infusion of 2400mg/m^2 over a 46-hour period every 2 weeks
Gem: Gem 100mg/m^2 BSA by 30-minute IV infusion weekly for 7 weeks, followed by a 1-week rest, then weekly for 3-weeks in subsequent 4-week courses</td><td>Gem+Cap: biweekly Gem 2200mg/m^2 as a 30 min IV infusion on Day 1 + oral capecitabine 2500mg/m^2/day in two equally divided daily doses approximately 12 hours apart from Days 1 to 7, repeated every 2 weeks for a maximum of 12 courses
Gem: biweekly Gem 2200mg/m^2 as a 30 min IV infusion on Day 1, repeated every 2 weeks for a maximum of 12 courses
NB: ondansetron 8mg was routinely given only on the day of IV chemotherapeutic drug administration</td><td>Nab-Pac+Gem: 30–40 minute IV infusion of Nab-Pac (125mg/m^2) followed by a 30–40 minute IV infusion of Gem (1,000 mg/m^2) on Days 1, 8, 15, 29, 36 and 43 of a 56-day cycle in Cycle 1 only and on Days 1, 8 and 15 of a 28-day cycle in Cycle 2 and onward.
Gem: 30–40 minute IV infusion of Gem (1,000 mg/m^2) on Days 1, 8, 15, 29, 36 and 43 of a 56-day cycle in Cycle 1 only and on Days 1, 8 and 15 of a 28-day cycle in Cycle 2 and onward.
Treatment continued until PD or unacceptable toxicity</td></tr>
<tr><td>Changes to treatment regimen</td><td>In the event of predefined toxic events, protocol-specified treatment modifications were permitted</td><td>Chemotherapeutic drug doses could be reduced by 25% or delayed with the occurrence of any severe non-haematological toxicity of low WBC and platelet counts</td><td>A maximum of two dose reductions were allowed from the original dose for toxicity management:
<table>
<tr><th>Dose level</th><th>Nab-Pac</th><th>Gem</th></tr>
<tr><td>Study dose</td><td>125mg/m^2</td><td>1,000mg/m^2</td></tr>
<tr><td>-1</td><td>100mg/m^2</td><td>800mg/m^2</td></tr>
<tr><td>-2</td><td>75mg/m^2</td><td>600mg/m^2</td></tr>
</table>
Following dose reduction, no dose re-escalation was permitted for the duration of the study.
Patients experiencing study drug-related AEs that required a dose delay >21 days were discontinued from further treatment.</td></tr>
<tr><td>Primary outcome</td><td>OS</td><td>PFS
Disease progression</td><td>OS</td></tr>
</table>

	ACCORD[7]	Scheithauer 2003[6]	CA046[12]
		measured using WHO criteria; independent assessment	
Secondary outcomes	PFS; tumour response; safety; QoL Disease progression measured using RECIST; independent assessment	OS and response rate; clinical benefit rate	PFS and ORR, assessed by an independent reviewer according to RECIST criteria; safety and tolerability of the administered treatments; investigator-assessed PFS and ORR
Survival follow-up	Median, months (95% CI): 26.6 (20.5–44.9) Death rate at final analysis: 79.8%	Randomisation: June 1999–May 2001	Death rate at final OS analysis: 80% Median follow-up was 9.1 months in the Nab-Pac+Gem group and 7.4 months in the Gem group. Death rate at updated post-hoc OS analysis: 90% (median follow-up was 13.9 months)

AE=adverse event; BSA=body surface area; CI=confidence interval; ECOG PS=Eastern Cooperative Oncology Group performance status; IV=intravenous; KPS=Karnofsky performance status; OS=overall survival; PD=progressive disease; PFS=progression-free survival; QoL=quality of life; RCT=randomised controlled trial; RECIST=Response Evaluation in Solid Tumours; ULN=upper limit of normal; WBC=white blood cell; WHO=World Health Organization
Source: Appendix 4 of the CS, adapted from Table 7 and Table 9; CS, adapted from Table 9; CS, page 55; CA046 original trial report[12]

10.6 Patient characteristics of studies in the reduced network of evidence

Table 56 Baseline characteristics of patients enrolled in studies in reduced network of evidence

	ACCORD		Scheithauer 2003		CA046	
	FOLFIRINOX (n=171)	**Gem (n=171)**	**Gem+Cap (n=41)**	**Gem (n=42)**	**Nab-Pac+Gem (n=431)**	**Gem (n=430)**
Age, median years (range)	61 (25–76)	61 (34–75)	64 (40–75)	66 (39–75)	62 (27-86)	63 (32-88)
Sex, male n (%)	106 (62.0)	105 (61.4)	27 (66)	23 (55)	245 (57)	257 (60)
Race, n (%)	NR	NR	NR	NR	Asian: 8 (2) Black: 16 (4) White: 378 (88) Hispanic: 25 (6) Other: 4 (1)	Asian: 9 (2) Black: 16 (4) White: 375 (87) Hispanic: 26 (6) Other: 4 (1)
Performance status, n (%)*	ECOG 0: 64 (37.4) ECOG 1: 106 (61.9) ECOG 2: 1 (0.6)	ECOG 0: 66 (38.6) ECOG 1: 105 (61.4) ECOG 2: 0	KPS 90-100: 11 (27) KPS 70-80: 22 (54) KPS 50-60: 8 (19)	KPS 90-100: 10 (24) KPS 70-80: 23 (55) KPS 50-60: 9 (21)	KPS 100: 69/429 (16) KPS 90: 179/429 (42) KPS 80: 149/429 (35) KPS 70: 30/429 (7) KPS 60: 2/429 (<1)	KPS 100: 69/429 (16) KPS 90: 199/429 (46) KPS 80: 128/429 (30) KPS 70: 33/429 (8) KPS 60: 0/429
Pancreatic tumour location, n (%)	Head: 67 (39.2) Body: 53 (31.0) Tail: 45 (26.3) Multicentric: 6 (3.5)	Head: 63 (36.8) Body: 58 (33.9) Tail: 45 (26.3) Multicentric: 5 (2.9)	NR	NR	Head: 191 (44) Body: 132 (31) Tail: 105 (24) Unknown: 3 (1)	Head: 180 (42) Body: 136 (32) Tail: 110 (26) Unknown: 4 (1)
Site of metastatic disease, n (%)**	Liver: 149/170 (87.6) Pancreas: 90/170 (52.9) Lymph node: 49/170 (28.8)	Liver: 150/171 (87.7) Pancreas: 91/171 (53.2) Lymph node: 39/171 (22.8)	Liver: 26 (63) Abdominopelvic mass: 32 (78) Lung: 9 (22)	Liver: 26 (62) Abdominopelvic mass: 27 (64) Lung: 6 (14)	Liver: 365 (85) Lung: 153 (35) Peritoneum: 19 (4)	Liver: 360 (84) Lung: 184 (43) Peritoneum: 10 (2)

	ACCORD		Scheithauer 2003		CA046	
	FOLFIRINOX (n=171)	**Gem (n=171)**	**Gem+Cap (n=41)**	**Gem (n=42)**	**Nab-Pac+Gem (n=431)**	**Gem (n=430)**
	Lung: 33/170 (19.4) Peritoneum: 33/170 (19.4) Other: 18/170 (10.6)	Lung: 49/171 (28.7) Peritoneum: 32/171 (18.7) Other: 29/171 (17.0)	Extra-abdominal lymph nodes/soft tissue: 2 (5) Adrenals: 2 (5) Spleen: 1 (2)	Extra-abdominal lymph nodes/soft tissues: 3 (7) Adrenals: 0 Spleen: 1 (2)		
Number of metastatic sites, n (%)	Median (range): 2 (1–6)	Median (range): 2 (1–6)	NR	NR	1 site: 33 (8) 2 sites: 202 (47) 3 sites: 136 (32) >3 sites: 60 (14)	1 site: 21 (5) 2 sites: 206 (48) 3 sites: 140 (33) >3 sites: 63 (15)
Level of CA19-9, n/N (%)	Normal: 24/164 (14.6) ULN to <59 x ULN: 72/164 (43.9) ≥59 ULN: 68/164 (41.5) Unknown: 7/171 (4.1)	Normal: 23/165 (13.9) ULN to <59 x ULN: 65/165 (39.4) ≥59 ULN: 77/165 (46.7) Unknown: 6/171 (3.5)	NR	NR	Normal: 60/379 (16) ULN to <59 x ULN: 122/379 (32) ≥59 ULN: 197/379 (52)	Normal: 56/371 (15) ULN to <59 x ULN: 120/371 (32) ≥59 ULN: 195/371 (53)
Presence of biliary stent, n (%)	Yes: 27 (15.8) No: 144 (84.2)	Yes: 22 (12.9) No: 149 (87.1)	10 (24)	7 (17)	80 (19)	68 (16)

*For CA046, KPS scores are presented as n/N (%); two patients in the Nab-Pac+Gem group had a score >70 at the screening visit but a score of 60 at the baseline visit on Day 1 or Cycle 1
** For ACCORD, site of metastatic disease is presented as n/N (%) where N is the number of patients with measurable metastatic sites
ECOG=Eastern Cooperative Oncology Group; KPS=Karnofsky performance status; NR=not reported; ULN=upper limit of normal
Source: Appendix 4 of the CS, adapted from Table 10 and Table 12; CS, adapted from Table 12

10.7 ERG summary of risk of bias of studies included in the base case network of evidence

The company considered that most trials were at a reasonably low risk of bias based on the assessment of selection bias, performance bias, attrition bias and detection bias. The ERG generally agrees with this statement, but notes that several of the included trials did not report important details concerning allocation concealment, blinding, and the extent of missing data.

The company's main concern related to the applicability of all trials to routine clinical practice in England. Specifically, the company judged five trials to be at high risk of bias due to the treatment setting not being representative of UK clinical practice, these trials were either conducted in Asia or compared regimens which are not currently used in UK clinical practice.

10.8 Quality assessment results for studies in the reduced network of evidence

Table 57 Quality assessment results for studies in the reduced network of evidence

Study question	ACCORD[7]		Scheithauer 2003[6]		CA046[12]	
	How is the question addressed in the study?	Risk of bias	How is the question addressed in the study?	Risk of bias	How is the question addressed in the study?	Risk of bias
Was randomisation carried out appropriately?	Yes. Randomisation was performed centrally in a 1:1 ratio with stratification according to centre, performance status (0 vs. 1), and primary tumour localisation (the head vs. the body or tail)	Low	Yes. Randomisation was stratified per KPS (90–100 vs. 50–80) and prior adjuvant treatment	Low	Yes. Randomisation schedule was generated by a randomisation statistician, with stratification for key prognostic factors.	Low
Was the concealment of treatment allocation adequate?	Unclear. No details provided	Unclear	Yes. Patients were assigned to treatment via a central office	Low	Yes. Randomisation was implemented via a centralised IVRS.	Low
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes. Overall patient demographics were well balanced; more patients in the FOLFIRINOX group had a biliary stent, more patients in the Gem group has measurable metastatic sites in the lung	Low	Yes. Baseline characteristics were well balanced between treatment groups	Low	Yes. Patient demographics were well balanced, with no key differences between treatment groups.	Low
Were the care providers, participants and outcome assessors blind to treatment allocation?	Unclear. No details provided	Unclear	Unclear. No details provided	Unclear	Independent assessors were blinded; care providers and participants were not.	Low
Were there any unexpected imbalances in drop-outs between groups?	Yes. More patients in the Gem group discontinued treatment, with almost twice as many patients discontinuing due to disease progression	High	No.	Low	No. The most common reason for study withdrawal in both treatment arms was disease progression, which is fully accounted for within efficacy assessments.	Low
Is there any evidence to suggest that the authors measured more	No.	Low	No.	Low	No.	Low

Study question	ACCORD[7]		Scheithauer 2003[6]		CA046[12]	
	How is the question addressed in the study?	Risk of bias	How is the question addressed in the study?	Risk of bias	How is the question addressed in the study?	Risk of bias
outcomes than they reported?						
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes. Efficacy analyses were performed according to the intention-to-treat principle	Low	Unclear. No details provided	Low	Yes. Efficacy analyses were performed according to the intention-to-treat principle, with standard censoring methods used to account for missing data.	Low
Did setting reflect UK practice?	Reasonably well. Although all patients were enrolled from French study centres, western Europe populations are considered generally comparable, and treatment arms and outcome assessments are reflective of UK practice.	Low	No. All patients were enrolled from study centres in Austria; comparator arm not reflective of UK practice and dosing of Gem monotherapy (2,200mg/m^2) not reflective of UK practice.	High	Not assessed by company	Not assessed by company

IVRS=interactive voice response system; KPS=Karnofsky performance status
Source: Appendix 4 of the CS, Table 14 and Table 16; CS, Table 12

10.9 Additional results from the network meta-analysis

For each analysis presented in the CS, the company provides results for each treatment included in the network versus Nab-Pac+Gem. However, as many of these treatments are of no relevance to the decision problem, throughout the following section the ERG presents results only for each of the treatments in the decision comparator set versus Nab-Pac+Gem.

Base case analysis

The company presents the results for each treatment included in the network versus Nab-Pac+Gem in Figure 10 (CS, p85), Figure 12 (CS, p88) and Figure 13 (CS, p89) of the CS for OS, PFS by independent assessment and PFS by investigator assessment, respectively.

For OS, Gem was shown to be statistically significantly inferior to Nab-Pac+Gem (HR=1.35, 95% CrI: 1.18 to 1.56). For Gem+Cap versus Nab-Pac+Gem, there is no evidence to suggest a difference between these two treatments in terms of OS. For FOLFIRINOX versus Nab-Pac+Gem, the HR favoured FOLFIRINOX, although this result was not statistically significant (HR=0.77, 95% CI: 0.58 to 1.01).

For PFS, Gem was shown to be statistically significantly inferior to Nab-Pac+Gem by both independent and investigator assessment. For Gem+Cap versus Nab-Pac+Gem, no statistically significant differences were observed between the treatments for PFS by either independent or investigator assessment. FOLFIRINOX was shown to be statistically significantly superior to Nab-Pac+Gem for PFS by independent assessment (HR=0.68, 95% CrI: 0.51 to 0.91). For PFS by investigator assessment, a trend in favour of FOLFIRINOX was observed, although this difference was no longer statistically significant (HR=0.77; 95% CI: 0.58 to 1.02).

SA1

The company presents the results of SA1 in Appendix 4 of the CS. For OS, estimated HRs for each of the treatments in the decision comparator set versus Nab-Pac+Gem are comparable to those observed in the base case analysis; however, there were no statistically significant differences between any of the treatments in the decision comparator set and Nab-Pac+Gem. Similarly, PFS by independent assessment results were comparable to those observed in the base case analysis; however, there were no statistically significant differences between any of the treatments in the decision comparator set and Nab-Pac+Gem.

SA3

For this analysis, the network of evidence is identical to the network used for the base case analysis, but data from two studies reporting median survival data for a metastatic pancreatic cancer subgroup are superseded with HR data from the total trial population. The company presents the results of SA3, which was performed for the outcome of OS only, in Appendix 4 of the CS.

10.10 Comparator method applied to model

The ERG has estimated OS and PFS for treatment with Gem+Cap and with FOLFIRINOX by applying HRs from relevant published papers [6,7] to the modelled OS and PFS estimates for Gem, which are based on data from the CA046 trial. This is in contrast to the company, which estimated OS and PFS for treatment with Gem+Cap and with FOLFIRINOX by combining HRs from relevant published papers [6,7] with HRs calculated from the CA046 trial and applying them to the modelled OS and PFS estimates for Nab-Pac+Gem, which are based on data from the CA046 trial. The difference in the approaches is illustrated by the following example.

If there are three treatments:

- treatment A (TxA) is the intervention of interest,
- treatment B (TxB) is a comparator and
- treatment C (TxC) is a comparator

and two trials:

- Trial 1 compares TxA and TxC, and
- Trial 2 compares TxB with TxC

then to compare TxA with TxB, there needs to be some sort of indirect comparison of effectiveness linked through TxC.

An NMA makes this comparison by first calculating HR_{AC} for TxA versus TxC from Trial 1 and HR_{BC} for TxB versus TxC from Trial 2. HR_{BC} is then adjusted by HR_{AC} to give HR_{AB}, an estimate of the effectiveness of TxA versus TxB (Figure 11).

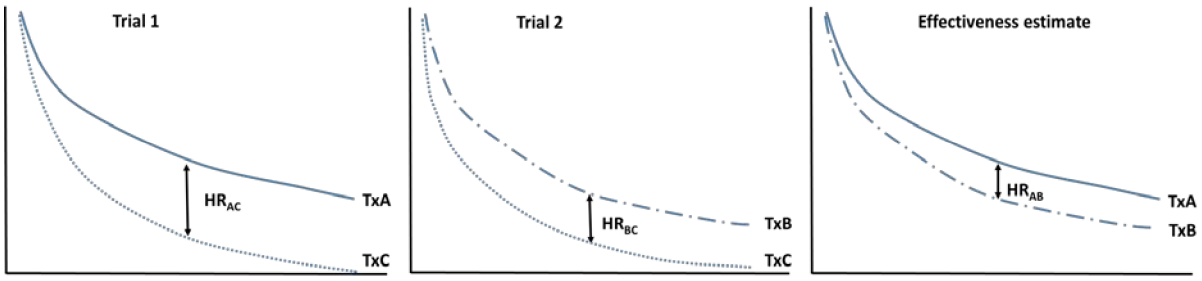

Figure 11 Simplified indirect comparison using HRs

Source: ERG
HR=hazard ratio; TxA=treatment A; TxB=treatment B; TxC=treatment C

This method of comparing the effectiveness of TxA with TxB requires that the PH assumption holds in both Trial 1 and Trial 2, as HRs are used from both these trials to calculate HR_{AB}.

If PH was shown not to hold in Trial 1 but could be shown to hold in Trial 2, an effectiveness comparison could be made between TxA and TxB in the cost effectiveness model by applying HR_{BC} from Trial 2 to the survival curve for TxC that had been estimated based on IPD from Trial 1.

10.11 PH test results FOLFIRINOX vs Gem and Gem+Cap vs Gem

A comparison of cumulative hazards on an H-H plot should yield an approximately straight line through the origin if hazards are proportional between the two treatments. A comparison of ln(-ln(OS)) or ln(-ln(PFS)) against ln(time) should yield approximately parallel lines if hazards are proportional between the two treatments. The comparisons are limited by the fact that the ERG has analysed data digitised from published papers,[6,7] so the following conclusions are based on visual inspection rather than statistical tests that might yield spurious precision.

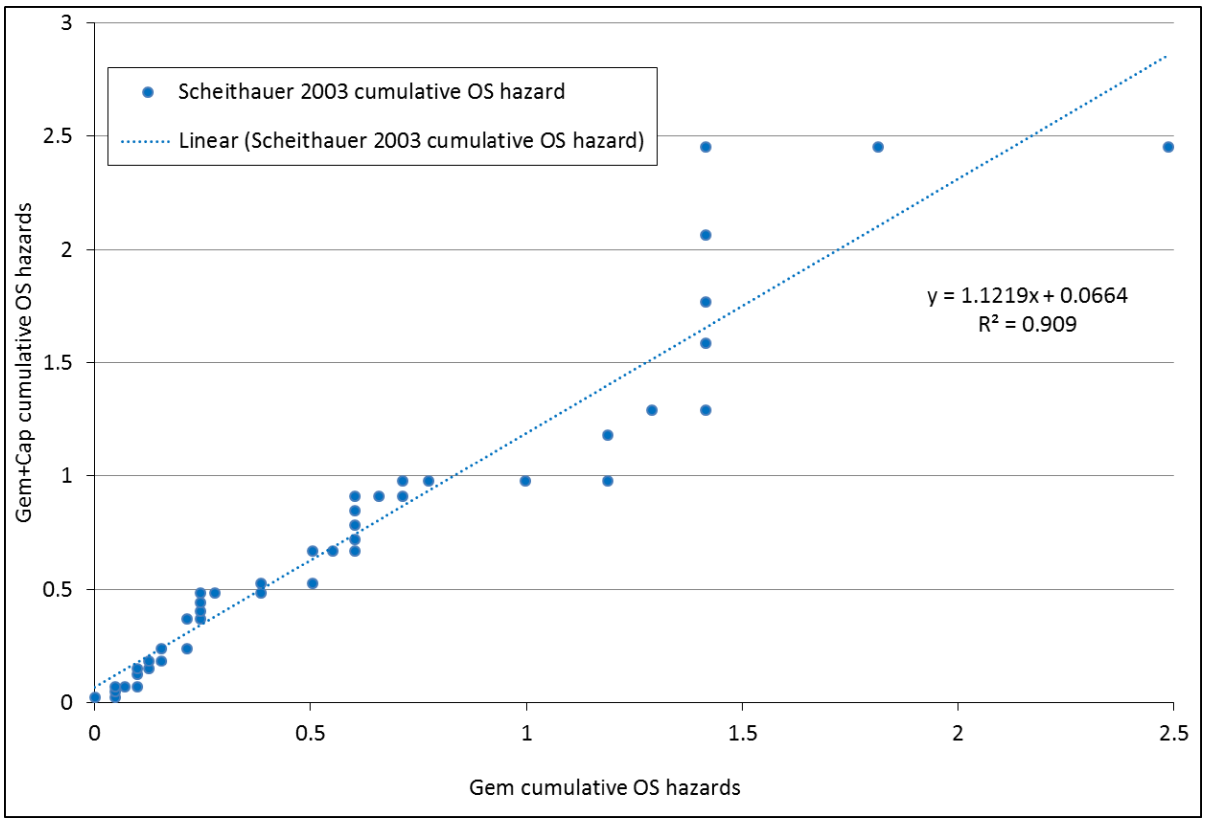

Figure 12 OS H-H plot Gem+Cap vs Gem

Source: ERG calculations; digitised data from Scheithauer 2003

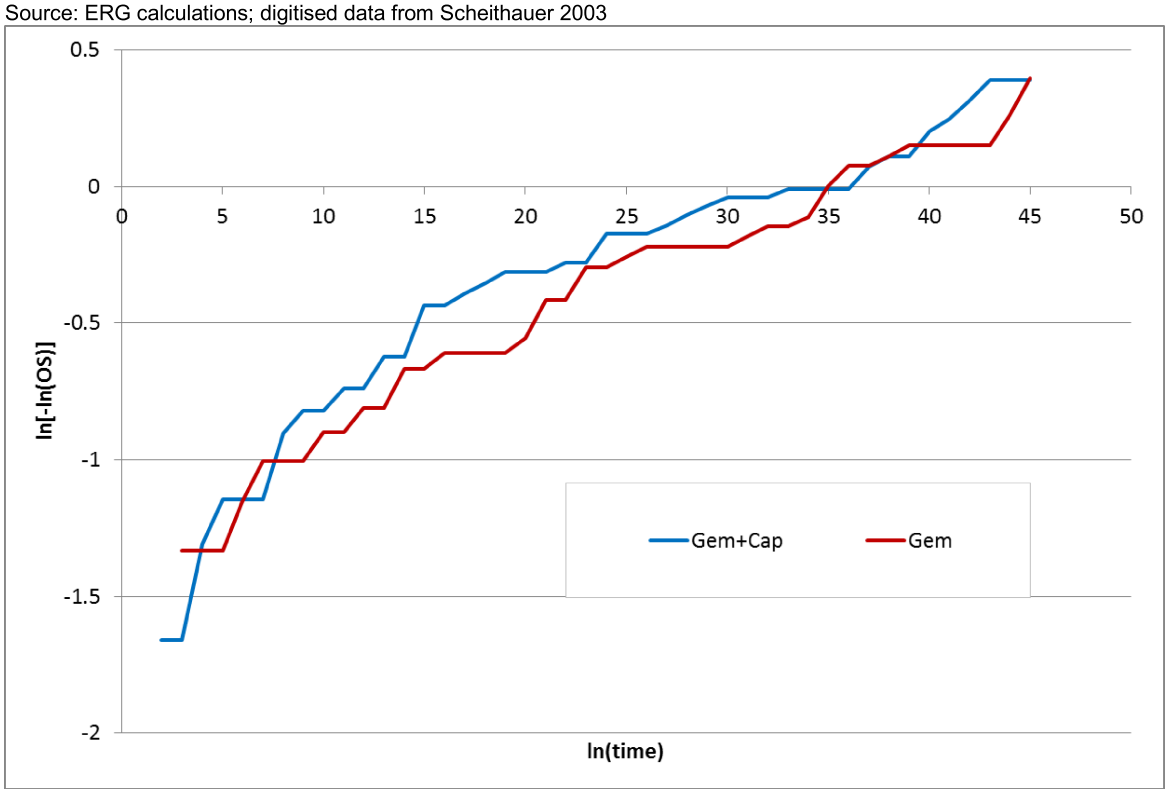

Figure 13 OS log-log plot Gem+Cap vs Gem

Source: ERG calculations; digitised data from Scheithauer 2003

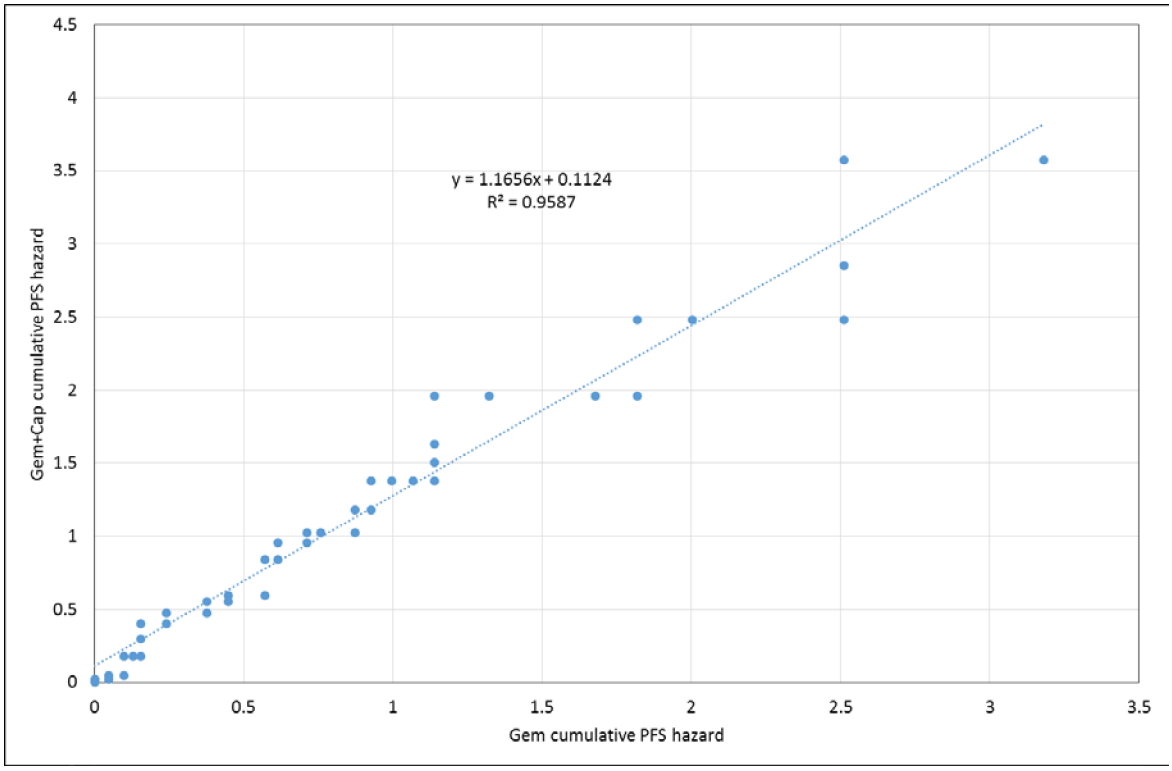

Figure 14 PFS H-H plot Gem+Cap vs Gem

Source: ERG calculations; digitised data from Scheithauer 2003

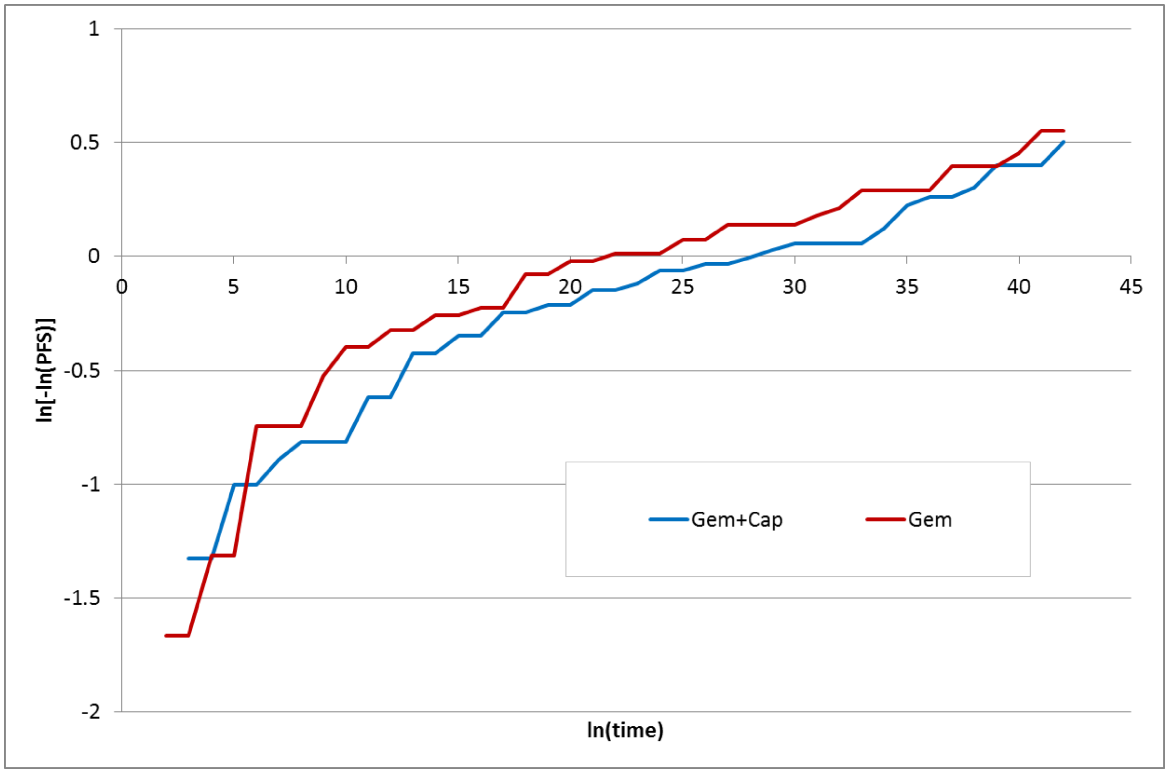

Figure 15 PFS log-log plot Gem+Cap vs Gem

Source: ERG calculations; digitised data from Scheithauer 2003

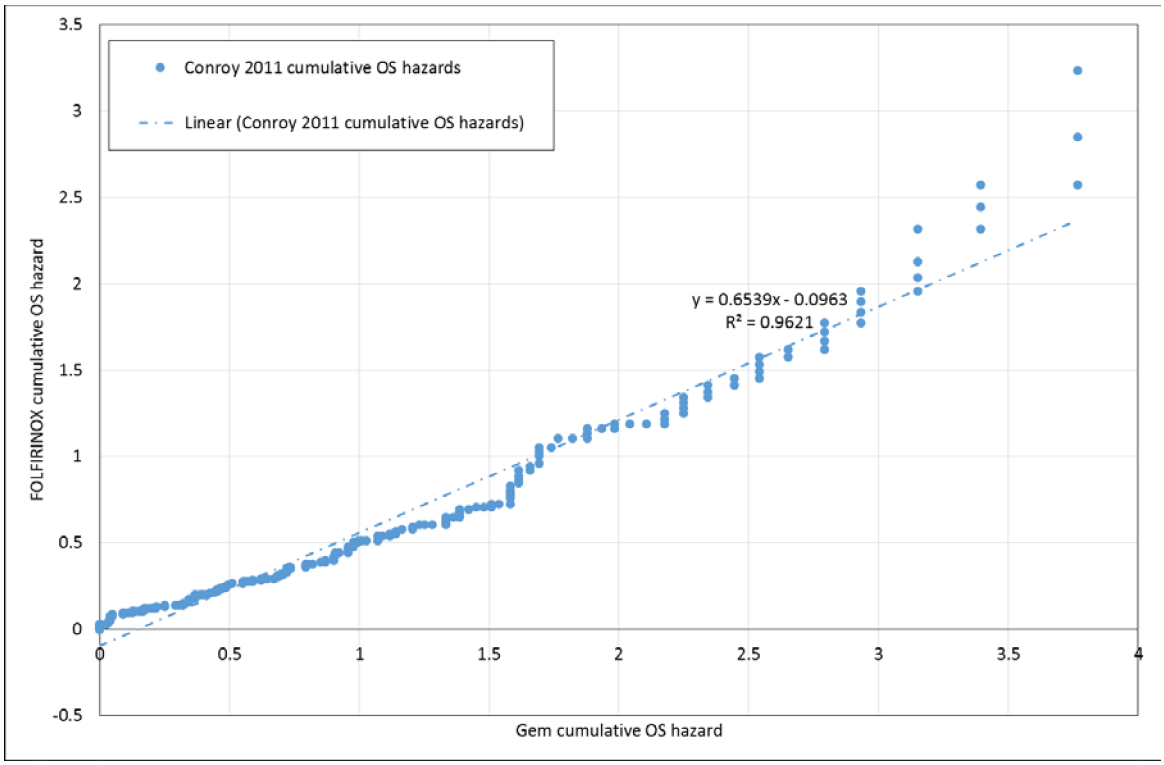

Figure 16 OS H-H plot FOLFIRINOX vs Gem

Source: ERG calculations using digitised data from Conroy 2011

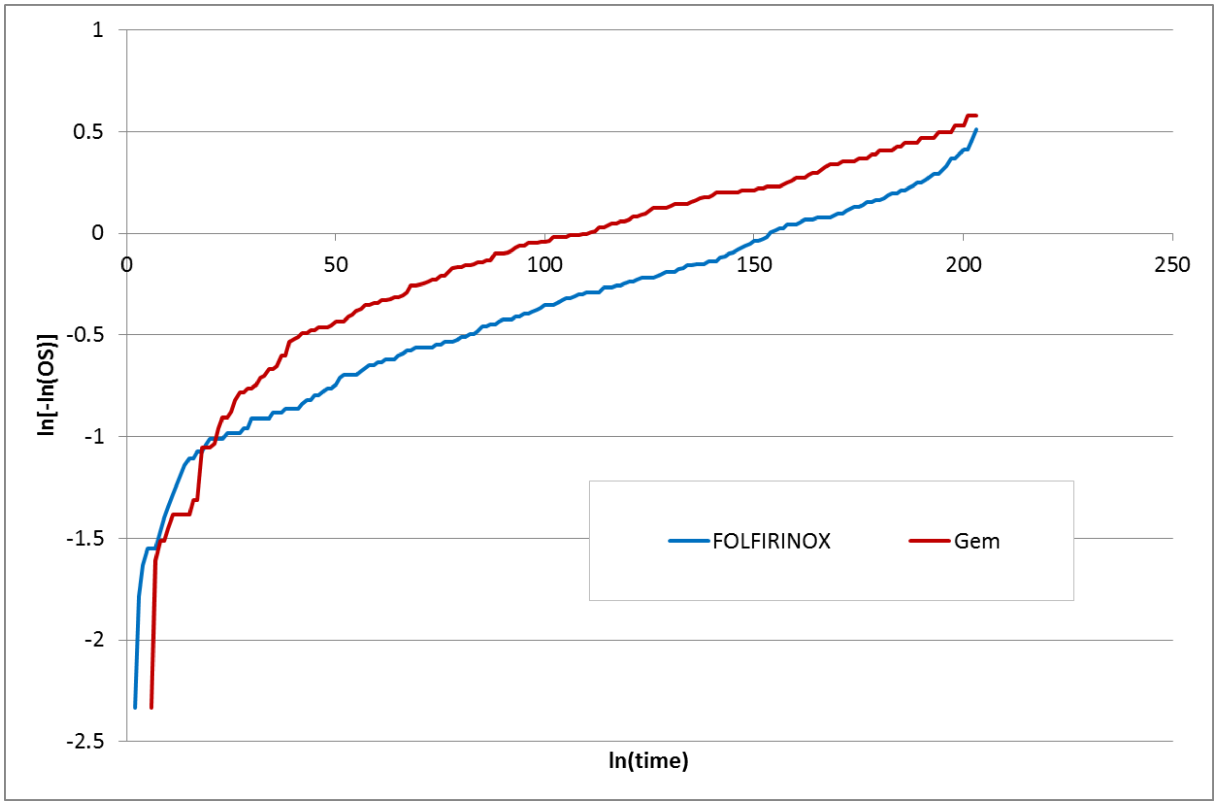

Figure 17 OS log-log plot FOLFIRINOX vs Gem

Source: ERG calculations using digitised data from Conroy 2011

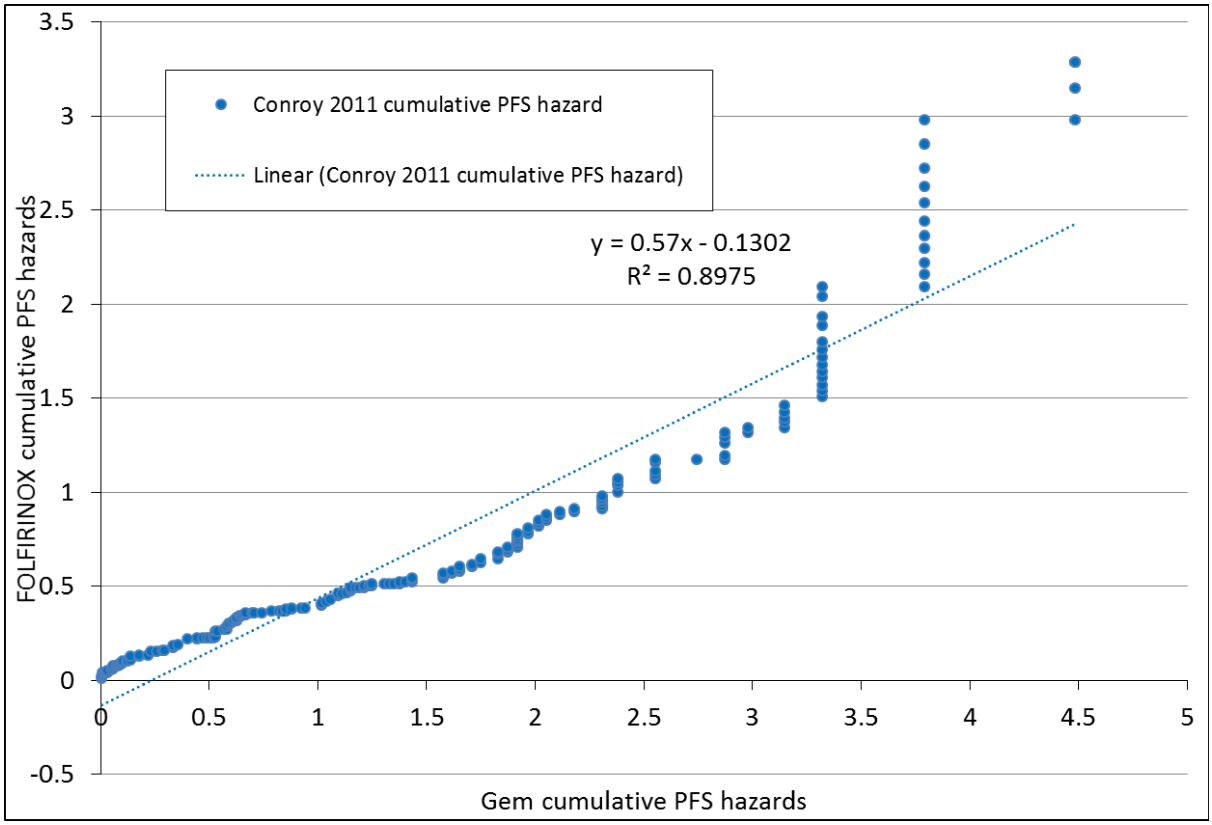

Figure 18 PFS H-H plot FOLFIRINOX vs Gem

Source: ERG calculations using digitised data from Conroy 2011

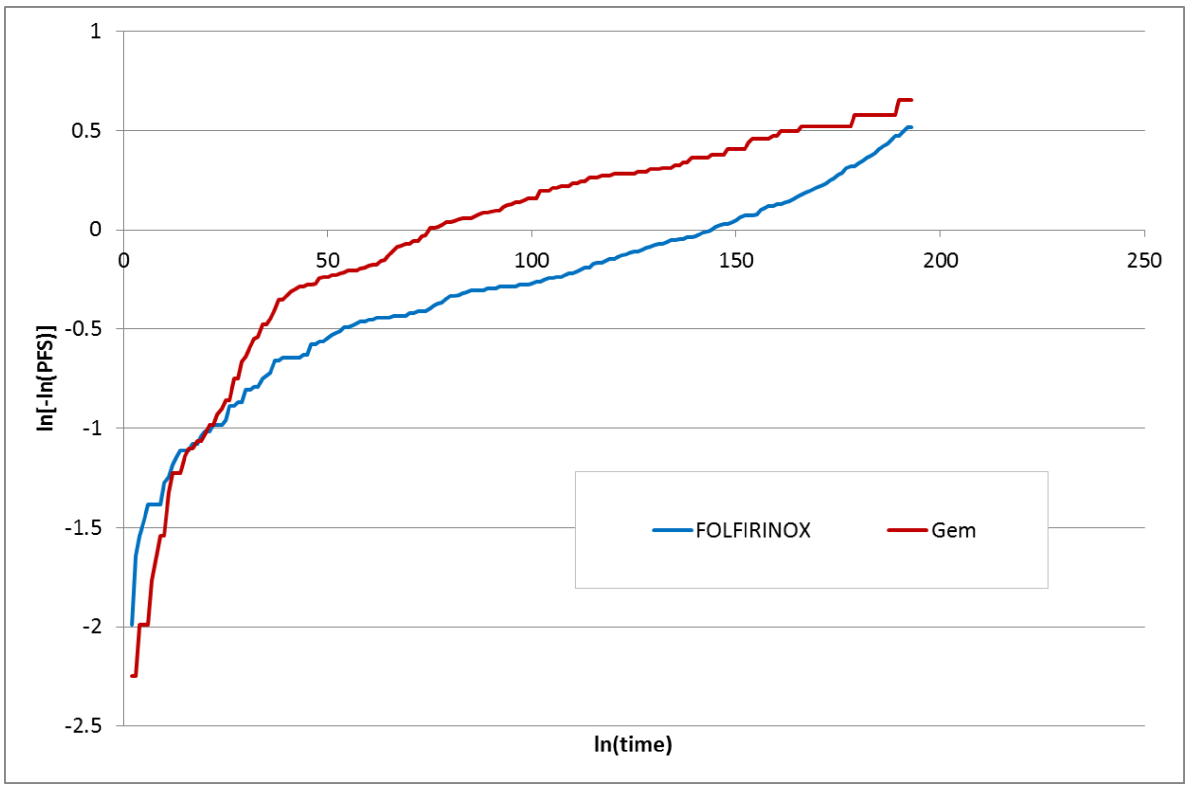

Figure 19 PFS log-log plot FOLFIRINOX vs Gem

Source: ERG calculations using digitised data from Conroy 2011

10.12 ERG Revisions to company's model

All revisions are activated by a logic switch. Logic switches are indicated by named range variables Mod_*letter* where letter = A - J.

A menu of revisions and Mod names appears below and on the 'Results' worksheet in the ERG amended model.

Instructions for modifying the updated company model (received during clarification)

1. Populate the following named switch values in the Results sheet

Revision #	Name	Switch value	Switch levels	Description
Correction	Mod_F	0	0, 1	Calculation of total LY and QALYs
R1	Mod_I	0	0, 1	HRs for Gem+Cap vs Gem
R2	Mod_B	0	0, 1	HRs for FOLFIRINOX vs Gem
R3	Mod_A	0	0, 1	ERG drug costing method
R4	Mod_E	0	0, 1	TOT from CA046 trial
R5	Mod_H	0	0, 1	Do not apply AE disutilities
R6	Mod_C	0	0, 1	ERG OS
R7	Mod_D	0	0, 1	ERG PFS
S1	Mod_G	0	0, 1	ERG AE costs
S2	Mod_J	0	0, 1	SIEGE crosswalk utility values *N.B. R5 (Mod_H) should also be applied*

2. Move all sheets from *ID1058_Nab-Pac_ERG additional model data.xlsx* into the model

3. Populate the following named ranges in the relevant sheets

Sheet	Value/formula	Name
OS	0.82	ERG_HR_OS_GemCap
OS	0.57	ERG_HR_OS_FOL
PFS	0.81	ERG_HR_PFS_GemCap
PFS	0.47	ERG_HR_PFS_FOL
ToT	0.81	ERG_HR_TOT_GemCap
ToT	0.47	ERG_HR_TOT_FOL

4. In sheet 'ToT', extend column AG to 522 cycles

5. In sheet 'Adverse_Events',
   - copy cells C45:C63
   - paste as values into cells R45:R63

6. For each sheet given in the 'Sheet' column below:
   - copy formulae from the 'Modified formulae' column in the table below
   - paste formulae into the cells referred to in the 'Cells' column in the table below

ERG revision number and description	Modification name	Sheet	Cells	Modified formulae
Correction	Mod_F	PF_Gem	Z15	=IF(Mod_F=0,1,0)*(O15*Cont.Cyclelength.PropYr*(p_u_stable+ae_gem_util))

ERG revision number and description	Modification name	Sheet	Cells	Modified formulae
			AA15	=IF(Mod_F=0,1,0)*((p_u_stable+IF(Control.2ndLineOption="Once patient has failed on 1st line treatment",ae_gem_doublet2l*ae_gemdoublet_util+ae_gem_mono2l*ae_mono2l_util+ae_gem_FOLF*ae_FOLFIRINOX_util,0)) *P15*Cont.Cyclelength.PropYr)
			AB15	=IF(Mod_F=0,1,0)*(Q15*Cont.Cyclelength.PropYr *(p_u_progressed+ae_gem_doublet2l*ae_gemdoublet_util+ae_gem_mono2l*ae_mono2l_util+ae_gem_FOLF*ae_FOLFIRINOX_util) +IF(cont.utility.decrement.duration="4 weeks", (R15*p_u_terminal_decrement*Cont.Cyclelength.PropYr), IF(cont.utility.decrement.duration="8 weeks", (S15*p_u_terminal_decrement*Cont.Cyclelength.PropYr), IF(cont.utility.decrement.duration="12 weeks", (T15*p_u_terminal_decrement*Cont.Cyclelength.PropYr),0))))
			AI15	=IF(Mod_F=0,O15*Cont.Cyclelength.PropYr,0)
			AJ15	=IF(Mod_F=0,P15*Cont.Cyclelength.PropYr,0)
			AK15	=IF(Mod_F=0,Q15*Cont.Cyclelength.PropYr,0)
Correction	Mod_F	PF_AbraxaneGem	X18	=IF(Mod_F=0,1,0)*(O18*Cont.Cyclelength.PropYr*(p_u_stable+ae_gemabx_util))
			Y18	=IF(Mod_F=0,1,0)*((p_u_stable+IF(Control.2ndLineOption="Once patient has failed on 1st line treatment",ae_gemabx_doublet2l*ae_gemdoublet_util+ae_gemabx_mono2l*ae_mono2l_util+ae_gemabx_FOLF*ae_FOLFIRINOX_util,0))*P18*Cont.Cyclelength.PropYr)
			Z18	=IF(Mod_F=0,1,0)*(Q18*Cont.Cyclelength.PropYr*(p_u_progressed+ae_gemabx_doublet2l*ae_gemdoublet_util+ae_gemabx_mono2l*ae_mono2l_util+ae_gemabx_FOLF*ae_FOLFIRINOX_util)+IF(cont.utility.decrement.duration="4 weeks",(R18*p_u_terminal_decrement*Cont.Cyclelength.PropYr),IF(cont.utility.decrement.duration="8 weeks",(S18*p_u_terminal_decrement*Cont.Cyclelength.PropYr),IF(cont.utility.decrement.duration="12 weeks",(T18*p_u_terminal_decrement*Cont.Cyclelength.PropYr),0))))
			AF18	=IF(Mod_F=0,1,0)*(O18*Cont.Cyclelength.PropYr)
			AG18	=IF(Mod_F=0,1,0)*(P18*Cont.Cyclelength.PropYr)
			AH18	=IF(Mod_F=0,1,0)*(Q18*Cont.Cyclelength.PropYr)
Correction	Mod_F	PF_GemCap	X15	=IF(Mod_F=0,1,0)*(O15*Cont.Cyclelength.PropYr*(p_u_stable+IF(Control.Rate.Equivalent.AE="Gemcitabine Monotherapy",ae_gem_util,ae_gemabx_util)))
			Y15	=IF(Mod_F=0,1,0)*((p_u_stable+IF(Control.2ndLineOption="Once patient has failed on 1st line treatment",ae_gemcap_doublet2l*ae_gemdoublet_util+ae_gemcap_mono2l*ae_mono2l_util+ae_gemcap_FOLF*ae_FOLFIRINOX_util,0))*P15*Cont.Cyclelength.PropYr)
			Z15	=IF(Mod_F=0,1,0)*(Q15*Cont.Cyclelength.PropYr*(p_u_progressed+ae_gemcap_doublet2l*ae_gemdoublet_util+ae_gemcap_mono2l*ae_mono2l_util+ae_gemcap_FOLF*ae_FOLFIRINOX_util)+IF(cont.utility.decrement.duration="4 weeks",(R15*p_u_terminal_decrement*Cont.Cyclelength.PropYr),IF(cont.utility.decrement.duration="8 weeks",(S15*p_u_terminal_decrement*Cont.Cyclelength.PropYr),IF(cont.utility.decrement.duration="12 weeks",(T15*p_u_terminal_decrement*Cont.Cyclelength.PropYr),0))))
			AC15	=IF(Mod_F=0,1,0)*(O15*Cont.Cyclelength.PropYr)
			AD15	=IF(Mod_F=0,1,0)*(P15*Cont.Cyclelength.PropYr)
			AE15	=IF(Mod_F=0,1,0)*(Q15*Cont.Cyclelength.PropYr)
Correction	Mod_F	PF_Fol	Z15	=IF(Mod_F=0,1,0)*(O15*Cont.Cyclelength.PropYr*(p_u_stable+ae_mono2l_util))

ERG revision number and description	Modification name	Sheet	Cells	Modified formulae
			AA15	=IF(Mod_F=0,1,0)*((p_u_stable+IF(Control.2ndLineOption="Once patient has failed on 1st line treatment",ae_FOLF_doublet2l*ae_gemdoublet_util+ae_folf_mono2l*ae_mono2l_util+ae_FOLF_FOLF*ae_FOLFIRINOX_util,0))*P15*Cont.Cyclelength.PropYr)
			AB15	=IF(Mod_F=0,1,0)*(Q15*Cont.Cyclelength.PropYr*(p_u_progressed+ae_FOLF_doublet2l*ae_gemdoublet_util+ae_folf_mono2l*ae_mono2l_util+ae_FOLF_FOLF*ae_FOLFIRINOX_util)+IF(cont.utility.decrement.duration="4 weeks",(R15*p_u_terminal_decrement*Cont.Cyclelength.PropYr),IF(cont.utility.decrement.duration="8nweeks",(S15*p_u_terminal_decrement*Cont.Cyclelength.PropYr),IF(cont.utility.decrement.duration="12 weeks",(T15*p_u_terminal_decrement*Cont.Cyclelength.PropYr),0))))
			AE15	=IF(Mod_F=0,1,0)*(O15*Cont.Cyclelength.PropYr)
			AF15	=IF(Mod_F=0,1,0)*(P15*Cont.Cyclelength.PropYr)
			AG15	=IF(Mod_F=0,1,0)*(Q15*Cont.Cyclelength.PropYr)
R1 HRs for Gem+Cap vs Gem	Mod_I	OS	E19:E541	=IF(Mod_I=0,1,0)*(C19^hr_os_GemCap)+IF(Mod_I=1,1,0)*(D19^ERG_HR_OS_GemCap)
R1 HRs for Gem+Cap vs Gem	Mod_I	PFS	E21:E543	=IF(Mod_I=0,1,0)*(C21^hr_pfs_GemCap)+IF(Mod_I=1,1,0)*(D21^ERG_HR_PFS_GemCap)
R1 HRs for Gem+Cap vs Gem	Mod_I	ToT	F20:F542	=IF(Mod_I=0,1,0)*(D20^hr_tot_GemCap)+IF(Mod_I=1,1,0)*(E20^ERG_HR_TOT_GemCap)
R2 HRs for FOLFIRINOX vs Gem	Mod_B	OS	F19:F541	=IF(Mod_B=0,1,0)*(C19^hr_os_FOL)+IF(Mod_B=1,1,0)*(D19^ERG_HR_OS_FOL)
R2 HRs for FOLFIRINOX vs Gem	Mod_B	PFS	F21:F543	=IF(Mod_B=0,1,0)*(C21^hr_pfs_FOL)+IF(Mod_B=1,1,0)*(D21^ERG_HR_PFS_FOL)
R2 HRs for FOLFIRINOX vs Gem	Mod_B	ToT	G20:G542	=IF(Mod_B=0,1,0)*(D20^hr_tot_FOL)+IF(Mod_B=1,1,0)*(E20^ERG_HR_TOT_FOL)
R3 ERG drug costing method	Mod_A	MoM_gem	BJ15:BJ537	=IF(Mod_A=0,IF(E15="","",(1-p_Perc_VialShare_Gem) *(AZ15*p_c_gem_1g+BA15*p_c_gem_200mg)+p_Perc_VialShare_Gem*BF15*c_gem_permg),IF(E15="","", (((1-p_Perc_VialShare_Gem) *ERG_weeklycost_gem_gem)+(p_Perc_VialShare_Gem*ERG_avgdose_gem_gem*ERG_costmg_gem_gem))* N15))

ERG revision number and description	Modification name	Sheet	Cells	Modified formulae
R3 ERG drug costing method	Mod_A	MoM_abxgem	CR15:CR537	=IF(Mod_A=0,IF(E15="","",(1-Perc_VialShare_Abx) *(BE15*p_c_abx_100mg+BF15*p_c_abx_250mg)+Perc_VialShare_Abx*CM15*c_abx_permg), IF(E15="","",(((1- Perc_VialShare_Abx)*ERG_weeklycost_npg_nabpac)+(Perc_VialShare_Abx*ERG_avgdose_npg_nabpac*ERG_costmg_npg_nabpac))*L15))
			CS15:CS537	=IF(Mod_A=0, IF(E15="", "", (1-p_Perc_VialShare_Gem) *(CA15*p_c_gem_1g+CB15*c_gem_200mg)+p_Perc_VialShare_Gem*CN15*c_gem_permg), IF(E15="","",(((1- p_Perc_VialShare_Gem)*ERG_weeklycost_npg_gem)+(p_Perc_VialShare_Gem*ERG_avgdose_npg_gem*ERG_costmg_npg_gem))*L15))
R3 ERG drug costing method	Mod_A	MoM_Cap	CC15:CC537	=IF(Mod_A=0,IF(E15="","", (L15*p_dose_cap*average_BSA*c_cap_permg)), IF(E15="","", (L15*ERG_weeklycost_gc_cap)))
			CE15:CE537	=IF(Mod_A=0, IF(E15="","",(1- p_Perc_VialShare_Gem)*(BU15*p_c_gem_1g+BV15*c_gem_200mg)+p_Perc_VialShare_Gem*BZ15*c_gem_permg), IF(E15="","",(((1- p_Perc_VialShare_Gem)*ERG_weeklycost_gc_gem)+(p_Perc_VialShare_Gem*ERG_avgdose_gc_gem*ERG_costmg_gc_gem))*L15))
R3 ERG drug costing method	Mod_A	MoM_FOLFIRINOX	CU15:CU537	=IF(Mod_A=0, IF($E15="","",(1- p_Perc_VialShare_Ox)*(AL15*p_c_ox_50mg+AM15*p_c_ox_100mg)+p_Perc_VialShare_Ox*CN15*c_ox_permg), IF($E15="","",(((1- p_Perc_VialShare_Ox)*ERG_weeklycosts_FOL_ox)+(p_Perc_VialShare_Ox*ERG_avgdose_FOL_ox*ERG_costmg_FOL_ox))*L15))
			CV15:CV537	=IF(Mod_A=0, IF($E15="","",(1- p_Perc_VialShare_flubol)*(AW15*p_c_flu_500mg+AV15*p_c_flu_250mg)+p_Perc_VialShare_flubol*$CO15*c_flu_permg), IF($E15="","",(((1- p_Perc_VialShare_flubol)*ERG_weeklycosts_FOL_5FUbol)+(p_Perc_VialShare_flubol*ERG_avgdose_FOL_5FUbol*ERG_costmg_FOL_5FUbol))*L15))
			CW15:Cw537	=IF(Mod_A=0, IF($E15="","",(1- p_Perc_VialShare_Flu)*(BC15*p_c_fluinf_2.5g+BD15*p_c_fluinf_5g)+p_Perc_VialShare_Flu*CP15*c_fluinf_permg), IF($E15="","",(((1- p_Perc_VialShare_Flu)*ERG_weeklycosts_FOL_5FUinf)+(p_Perc_VialShare_Flu*ERG_avgdose_FOL_5FUinf*ERG_costmg_FOL_5FUinf))*L15))

ERG revision number and description	Modification name	Sheet	Cells	Modified formulae
			CX15:CX537	=IF(Mod_A=0, IF($E15="","",(1-p_Perc_VialShare_leu)*(BR15*p_c_leu_100mg+BS15*p_c_leu_300mg)+p_Perc_VialShare_leu*CQ15*c_fa_permg), IF($E15="","",(((1-p_Perc_VialShare_leu)*ERG_weeklycosts_FOL_folac)+(p_Perc_VialShare_leu*ERG_avgdose_FOL_folac*ERG_costmg_FOL_folac))*L15))
			CY15:Cy537	=IF(Mod_A=0, IF($E15="","",(1-p_Perc_VialShare_Iri)*(CB15*p_c_Iri_100mg+CC15*p_c_Iri_300mg)+p_Perc_VialShare_Iri*CR15*c_iri_permg), IF($E15="","",(((1-p_Perc_VialShare_Iri)*ERG_weeklycosts_FOL_iri)+(p_Perc_VialShare_Iri*ERG_avgdose_FOL_iri*ERG_costmg_FOL_iri))*L15))
R4 TOT from CA046 trial	Mod_E	ToT	D20:D542	=IF(Mod_E=0,1,0)*IF(Control.ToT.Curve="KM Data",L123,AU16)+IF(Mod_E=1,1,0)*VLOOKUP(C20,ERG_TTE_basecase,5)
			E20E542	=IF(Mod_E=0,1,0)*IF(Control.ToT.Curve="KM Data",M123,AV16)+IF(Mod_E=1,1,0)*VLOOKUP(C20,ERG_TTE_basecase,6)
R5 Do not apply AE disutilities	Mod_H	Controls	F56	Change company switch to 'No'
R6 ERG OS	Mod_C	Controls	F34	Change company switch to 'ERG curves'
R7 ERG PFS	Mod_D	Controls	F38	Change company switch to 'ERG curves'
S1 ERG AE costs	Mod_G	Adverse Events	C45	=IF(Mod_G=0, 1,0)*R45+IF(Mod_G=1, 1,0)*ERG_neutro
			C46	=IF(Mod_G=0, 1,0)*R46+IF(Mod_G=1, 1,0)*ERG_fatigue
			C47	=IF(Mod_G=0, 1,0)*R47+IF(Mod_G=1, 1,0)*ERG_thrombo
			C48	=IF(Mod_G=0, 1,0)*R48+IF(Mod_G=1, 1,0)*ERG_anaemia
			C49	=IF(Mod_G=0, 1,0)*R49+IF(Mod_G=1, 1,0)*ERG_leuko
			C50	=IF(Mod_G=0, 1,0)*R50+IF(Mod_G=1, 1,0)*ERG_psensneuro
			C51	=IF(Mod_G=0, 1,0)*R51+IF(Mod_G=1, 1,0)*ERG_neuroperi
			C52	=IF(Mod_G=0, 1,0)*R52+IF(Mod_G=1, 1,0)*ERG_dehydra
			C53	=IF(Mod_G=0, 1,0)*R53+IF(Mod_G=1, 1,0)*ERG_asthenia
			C54	=IF(Mod_G=0, 1,0)*R54+IF(Mod_G=1, 1,0)*ERG_abdopain
			C55	=IF(Mod_G=0, 1,0)*R55+IF(Mod_G=1, 1,0)*ERG_nausea
			C56	=IF(Mod_G=0, 1,0)*R56+IF(Mod_G=1, 1,0)*ERG_diarrhoea
			C57	=IF(Mod_G=0, 1,0)*R57+IF(Mod_G=1, 1,0)*ERG_vomiting
			C58	=IF(Mod_G=0, 1,0)*R58+IF(Mod_G=1, 1,0)*ERG_decappetite
			C59	=IF(Mod_G=0, 1,0)*R59+IF(Mod_G=1, 1,0)*ERG_pulembo

ERG revision number and description	Modification name	Sheet	Cells	Modified formulae
			C60	=IF(Mod_G=0, 1,0)*R60+IF(Mod_G=1, 1,0)*ERG_pneumonia
			C61	=IF(Mod_G=0, 1,0)*R61+IF(Mod_G=1, 1,0)*ERG_febneutro
			C62	=IF(Mod_G=0, 1,0)*R62+IF(Mod_G=1, 1,0)*ERG_cholangitis
			C63	=IF(Mod_G=0, 1,0)*R63+IF(Mod_G=1, 1,0)*ERG_hyperbili
S2 SIEGE crosswalk utility values	Mod_J	Controls	F54	Change company switch to 'SIEGE study (Crosswalk)'